

# **PUBLIC SUMMARY DOCUMENT**

**Product:** Multicomponent Meningococcal Group B Vaccine, 0.5mL, injection, prefilled syringe, Bexsero®.

**Sponsor:** Novartis Vaccines and Diagnostics Pty Ltd.

**Date of PBAC Consideration:** November 2013

## **1. Purpose of Application**

To request the inclusion of 4-component meningococcal group B vaccine (4CMenB) in the National Immunisation Program (NIP) Schedule for prevention of meningococcal B disease in infants and adolescents.

## **2. Background**

This was the first submission to the PBAC for inclusion of 4CMenB in the NIP.

## **3. Registration Status**

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.

## **4. Listing Requested and PBAC's View**

The submission requested inclusion of 4CMenB in the NIP with a proposed vaccination schedule as a routine 3+1 schedule in infants, a 2 dose course in adolescents and a catch-up program in older infants, toddlers and adolescents. .

The requested NIP listing is consistent with the TGA-approved indication.

## **5. Clinical Place for the Proposed Therapy**

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. Data collected between 1991 and 2011 indicates that incidence is bimodal, with 20% of confirmed cases aged <1 year, 22% aged 1-4 years, and the next peak in later teens, with 17% aged 15-19 years and 9% aged 20 to 24 years. Applying this pattern, around 5 of the deaths in 2011 were in those aged <5 years. 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 low incidence of IMD, asymptomatic carriage of meningococci (all serotypes) is common: from 4,500 per 100,000 in infants to a peak of 23,000 per 100,000 in 19-year olds.

The vaccine contains four antigenic components, adsorbed on aluminium hydroxide: factor H binding protein (fHbp), neisserial adhesin A (NadA), neisseria heparin binding antigen (NHBA) and outer membrane vesicles (OMV) from a New Zealand epidemic strain (NZ98/254), which provides PorA P1.4. 4CMenB is intended to stimulate the production of bactericidal antibodies that recognise these antigens, and protect against a broad range of disease-causing meningococcal group B strains.

The PBAC considered that the vaccine was an important advance in vaccinology, using new technology to address issues specific to meningococcal B. While there are conjugate based and polysaccharide capsule-based vaccines currently available for other meningococcal groups, similar approaches for meningococcal B vaccines have failed because the

meningococcal B polysaccharide capsule is poorly immunogenic. 4CMenB was created using an innovative approach to vaccine development known as reverse vaccinology. This process employs genomic mining to identify multiple surface-exposed antigens that are important virulence factors and that are believed to be highly conserved across most isolates.

The PBAC noted the Australian Technical Advisory Group on Immunisation (ATAGI) post-submission advice that considered although there may be clinical value in a targeted program for indigenous children aged <5 years, and patients with complement deficiency and asplenia, based on increased risk of IMD, there are significant implementation issues to consider in the delivery of programs that target specific sub-populations. In particular, that coverage is difficult to predict, and has historically been low for other targeted vaccine programs. The submission did not consider the clinical benefit or cost-effectiveness of targeting the vaccine to any high risk population.

## 6. Comparator

The submission nominated no vaccination as the comparator.

The PBAC agreed that the nominated comparator was appropriate, given that no vaccine against meningococcal B infection is currently available.

## 7. Clinical Trials

The submission presented separate studies to support vaccine efficacy in infants and in adolescents. All of the studies presented in the submission use a surrogate marker of vaccine efficacy (namely titres of  $\geq 1:4$  derived from a human serum bactericidal assay (hSBA)), historically accepted for establishing protection from meningococcal disease. No clinical outcome studies were conducted. The PBAC recalled that it had accepted the use of SBA titres, as a surrogate outcome for clinical efficacy, in its consideration of the combination vaccine for *Haemophilus influenzae* (Hib) and *Neisseria meningitidis* serogroup C (MenC) compared to giving the two component vaccines concomitantly. The PBAC noted that the threshold titre value was determined based on studies from the 1960s assessing the bactericidal activity of an Army recruit population for susceptibility to group C meningococcal disease. The PBAC also noted that all previous meningococcal vaccines validated with effectiveness outcomes using this surrogate have been based upon capsular polysaccharide antigens, with or without glycoconjugation. The PBAC noted that ATAGI agreed that the use of an hSBA titre threshold of  $\geq 1:4$  is a suitable surrogate for inference of the clinical efficacy of the 4CMenB vaccine in clinical trials.

**Infants:** The submission presented two randomised trials comparing 4CMenB to placebo (Studies V72P12 and V72P13), in infants aged 2 months at entry, receiving 3 doses. A meta-analysis of these trials is also presented in support of the clinical claim for vaccination in infants. The submission presented additional evidence from 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 is presented in support of the clinical claim for a booster dose at 12 months of age.

The PBAC noted that these studies were carried out with the routine concomitant vaccinations of Infanrix Hexa, Prevenar 7 and MMRV, but not rotavirus or Prevenar 13 which are currently on the NIP for infants. There is no information on potential interaction of the 4CMenB with rotavirus or some pneumococcal serotypes contained in Prevenar 13 in terms of protective immune response or potential harms.

A supportive trial, Study V72P16, investigated the impact of prophylactic paracetamol following concomitant administration of 4CMenB with the routine vaccines in infants at 2, 3 and 4 months of age.

**Adolescents:** The submission presented one randomised trial comparing 4CMenB to placebo (Study V72P10), in adolescents 11 to 17 years of age, receiving 1, 2 or 3 doses. The submission presented additional evidence from one extension study, V72P10E1 to demonstrate persistence of effect.

**Carriage:** The submission presented one randomised trial 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).

Details of the trials and associated reports presented in the submission are presented in the table below.

**Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Infant Studies</b>		
V72P12	<p>Gossger N, Snape MD, Finn A et al. Immunogenicity of an investigational multicomponent meningococcal serogroup B vaccine (4CMenB) administered with or without routine infant vaccinations in different schedules.</p> <p>Gossger, N., Snape, M. D., et al. (2012). "Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: A randomized controlled trial."</p> <p>Cohn, A. C. and Messonnier, N. E. (2012). "Inching toward a serogroup B meningococcal vaccine for infants."</p> <p>Vesikari, T., S. Esposito, et al. (2013). "Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: Results of two randomised trials."</p> <p>Beeretz I, Snape MD, Finn A et al. Reactogenicity and safety of multicomponent meningococcal serogroup B vaccine (4CMenB) administered with or without routine infant vaccinations in different schedules.</p>	<p>Poster presented at 29th ESPID Meeting, 7-11 June 2011, The Hague, The Netherlands.</p> <p>JAMA - Journal of the American Medical Association 307(6): 573-582</p> <p>JAMA - Journal of the American Medical Association 307(6): 614-615.</p> <p>The Lancet 381(9869): 825-835.</p> <p>Poster No. 1187. Presented at 29th ESPID Meeting, 7-11 June 2011, The Hague, The Netherlands.</p>
V72P12E1	<p>Snape, MD, Finn A, Heath et al. Persistence to 12, 18 and 24 months of bactericidal antibodies induced by infant immunisation with a serogroup B meningococcal vaccine.</p>	<p>Poster presented at 31st ESPID Meeting, May 28-June 1 2013, Milan, Italy.</p>
V72P13		

	<p>Vesikari, T., Esposito, S., et al. (2010). "Immunogenicity of an investigational multicomponent meningococcal serogroup B vaccine in healthy infants at 2, 4 and 6 months of age."</p> <p>Vesikari, T., Esposito, S., et al. (2011). "Use of an investigational multicomponent meningococcal serogroup B vaccine (4cmenb) in a clinical trial in 3630 infants."</p> <p>Vesikari, T., S. Esposito, et al. (2013). "Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: Results of two randomised trials."</p>	<p>Canadian Journal of Infectious Diseases and Medical Microbiology 21(4): 183</p> <p>Archives of Disease in Childhood 96: A3.</p> <p>The Lancet 381(9869): 825-835.</p>
V72P13E1	<p>Vesikari T, Prymula R, Liese J et al. Booster dose at 12 months of an investigational meningococcal serogroup B vaccine (4CMenB) in healthy toddlers previously primed at 2,4,6 months.</p> <p>Prymula R, Vesikari T, Esposito S, et al. Catch-up vaccination of healthy toddlers with an investigational meningococcal serogroup B vaccine (4CMenB) - exploration of a two-dose schedule.</p> <p>Toneatto D, Prymula R, Merrall E et al. Immunogenicity and reactogenicity of two-dose vaccination with investigational meningococcal b recombinant vaccine at 24 and 26 months of age.</p>	<p>Poster presented at 29th ESPID Meeting, 7-11 June 2011, The Hague, The Netherlands.</p> <p>Poster presented at 29th ESPID Meeting, 7-11 June 2011, The Hague, The Netherlands.</p> <p>Poster presented at 31st ESPID Meeting, May 28-June 1 2013, Milan, Italy.</p>
<b>Adolescent Studies</b>		
V72P10	<p>Santolaya, M. E., O'Ryan, M. L., et al. (2012). "Immunogenicity and tolerability of a multicomponent meningococcal serogroup B (4CMenB) vaccine in healthy adolescents in Chile: A phase 2b/3 randomised, observer-blind, placebo-controlled study."</p> <p>Stephens, D. S. (2012). "Prevention of serogroup B meningococcal disease."</p>	<p>The Lancet 379(9816): 617-624.</p> <p>The Lancet 379(9816): 592-594.</p>
V72P10E1	<p>Santolaya ME, O'Ryan MO, Valenzuela MT et al. Persistence of antibodies 18–24 months after adolescent immunization with 1–3 doses of a multicomponent meningococcal serogroup B vaccine.</p> <p>Santolaya ME, O'Ryan M, Dull, P. et. al. Persistence of antibodies in adolescents 18–24 mo after immunization with one, two or three doses of 4CMenB meningococcal serogroup B vaccine.</p>	<p>Poster presented at 31st ESPID Meeting, May 28-June 1 2013, Milan, Italy.</p> <p>Human Vaccines &amp; Immuno. Vol 9 Issue 11 June 2013 (e-pub ahead of print)  <a href="http://www.landesbioscience.com/journals/vaccines/article/25505/">http://www.landesbioscience.com/journals/vaccines/article/25505/</a></p>

## 8. Results of Trials

The hSBA titre was measured in the sera of vaccinees against indicator bacterial strains, corresponding to antigens in the vaccine. Since the completion of the study, the sponsor identified a candidate serogroup B indicator strain (M10713) for measuring antigen-specific hSBA responses to the NHBA antigen. Post-hoc analyses were conducted on a small number of sera from the trials.

Indicator strain	Antigen component of 4CMenB
44/76	fHbp
5/99	NadA
NZ98/254	PorA P1.4
M10713	NHBA

### Infants – Primary vaccination schedule:

The submission presented a meta-analysis of studies V72P12 and V72P13 of the primary endpoint (percentage of participants with hSBA  $\geq 1:5$ ).

The PBAC noted that the primary objective was met for both studies against the three antigen strains in the pre-specified analysis (fHbp, NadA and PorA P1.4). The proportion of vaccinated infants achieving a hSBA  $\geq 1:5$  against antigen PorA P1.4 was less than for antigens fHbp and NadA. The PBAC noted the ATAGI observation (pre-PBAC Submission Advice, June 2013) that the proportion of participants with hSBA  $\geq 1:5$  against antigen PorA P1.4 is ‘lesser, but still acceptably high’. Post-hoc analyses were conducted in trials V72P12 (N= 36-39) and V72P13 (N= 100) to assess hSBA response against antigen NHBA. Using the lower limit of the 95% CI for the % of subjects with hSBA titer  $>1:5$  of  $\geq 70\%$  to determine sufficient immune response, results from Study V72P13 met the criteria for antigen NHBA. Post-hoc analysis of participants from Study V72P12 did not meet the criteria for sufficient immune response as that the response 1 month after the 3<sup>rd</sup> immunisation was similar to baseline levels.

### Infants – Booster dose:

Results for the primary endpoint (percentage of participants with hSBA  $\geq 1:5$ ) at one month after the third vaccination, including the results of post-hoc analyses conducted against antigen NHBA amongst 100 participants in Trial V72P13 and V72P13E1 are presented in the table below.

#### Number of participants with bactericidal titres (hSBA) $\geq 1:5$ , Study V72P13 and V72P13E1: PP, MITT for M10713 (NHBA)

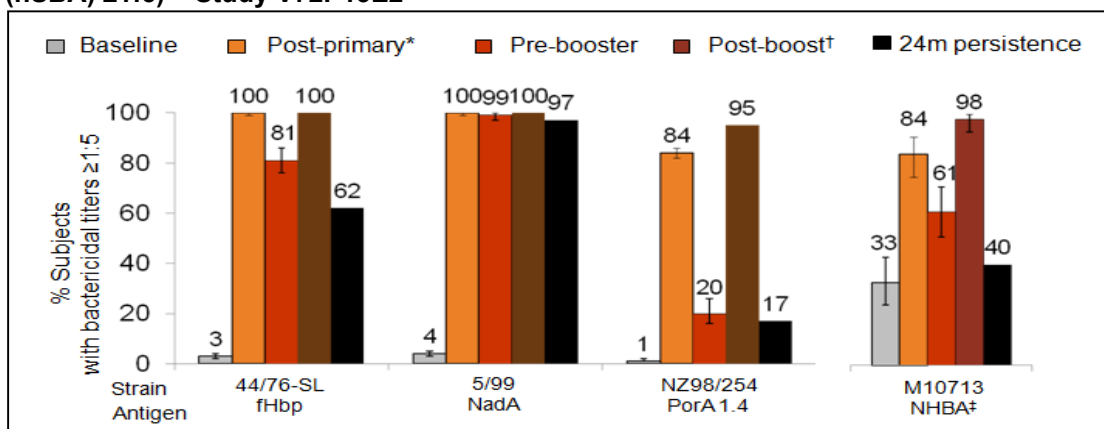
Study	Strain	44/76 (fHbp)	5/99 (NadA)	NZ98/254 (PorA P1.4)	M10713 <sup>d</sup> (NHBA)
V72P13 4CMenB All (246) <sup>a</sup>	Baseline n (%) 95% CI	35 (3%) (2-4) N=1,156	45 (4%) (3-5) N=1,154	14 (1%) (1-2) N=1,160	33 (33%) (24-43) N=100
	1 month after 3rd dose	1,146 (100%) (99-100) N=1,149	1,149 (100%) (99-100) N=1,152	965 (84%) (82-86) N=1,152	84 (84%) (75-91) N=100
V72P13E1	6 months after 3rd	348 (82%)	418 (99%)	93 (22%)	61 (61%)

Men246 <sup>b</sup>	dose (prebooster)	(78-85) N=426	(97-100) N=423	(18-26) N=426	(51-71) N=100
	1 month after booster	422 (100%) (99-100) N=422	421 (100%) (99-100) N=421	404 (95%) (93-97) N=424	98 (98%) (93-100) N=100

CI: confidence interval; MITT: modified intention to treat; N: total number of participants; PP: per protocol population. **a** 4CMenB All (246), combined lots of 4CMenB administered at 2, 4 and 6 months. **b** 12B12M (1a) + 12B13M (1b) combined: in the open-label (immunogenicity) subset of V72P13, these participants had received 4CMenB + routine vaccinations at 2, 4 and 6 months of age. In V72P13E1, these participants received a 4CMenB booster and MMRV at 12 or 13 months of age. **d** Since the completion of the study, Novartis has identified a candidate serogroup B indicator strain (M10713) for measuring antigen-specific hSBA responses to the NHBA antigen (post-hoc immunogenicity endpoint)(MITT results).

The results observed in V72P13/E1 reflected the comparative benefits of vaccination of infants. The PBAC noted that similar results were observed in V72P12E1. Significant variation of bacterial antibody response was observed across antigens at each time point tested. The persistence of bacterial antibody 6 months after the 3<sup>rd</sup> dose and 12 months post-booster varied across the antigens. There is a considerable decline in the proportion of vaccine recipients with bactericidal antibody titres, particularly against antigens PorA P1.4 and NHBA.

#### 4CMenB given at 2, 4, 6, and 12 months (percentage of participants with bactericidal titres (hSBA) $\geq 1:5$ ) – Study V72P13E2



Post-primary: 1 month after 3<sup>rd</sup> dose, Pre-booster: vaccinees at 12 months of age (6 months after 3<sup>rd</sup> dose), Post-booster: 1 month after booster, 24m persistence: 12 months after booster dose.

The PBAC noted the rapid waning of titres after primary infant series and after the booster given at 12 months of age. The PBAC noted in a recent publication (Snape MD et al, Persistence of bactericidal antibodies following early infant vaccination with a serogroup B meningococcal vaccine and immunogenicity of a preschool booster dose. 2013 CMAJ 185:E7-24) that there was some anamnestic response at age 40-44 months for infants who received 4 doses. The PBAC considered the key correlate of protection was persistent circulating bactericidal antibodies at adequate levels, which was not supported by the data presented in the submission.

#### Adolescents, – Primary vaccine schedule:

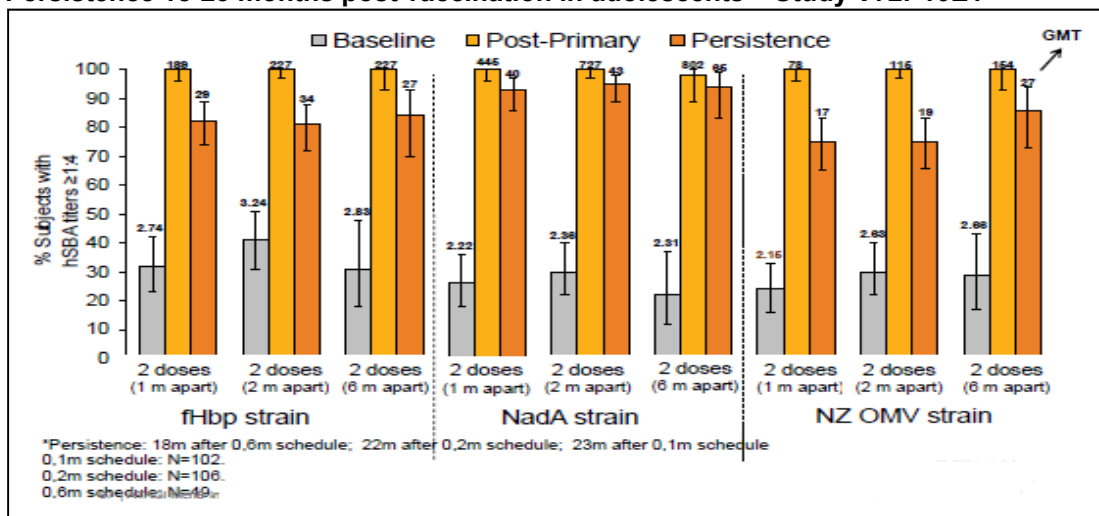
The submission presented results for the primary endpoint (percentage of participants with hSBA  $\geq 1:4$ ).

The baseline (pre-vaccination) proportion of all trial participants with a titre of  $\geq 1:4$  was 30-46%, against fHbp, NadA and PorA P1.4. Analysis of NHBA was a post-hoc analysis, with a small sample size and at baseline a higher percentage of subjects were already seropositive

for NHBA. The PBAC considered the effect of the vaccine may be confounded by the high baseline antibody responses.

Following two doses, either 1 or 2 months apart (as the proposed NIP schedule), 100% of participants had hSBA titres  $\geq 1:4$  one month after the second dose. Ninety-three percent of participants had hSBA titres  $\geq 1:4$  one month after a single dose. At 18-23 months after the last 4CMenB vaccine dose when given as a two dose vaccination schedule, 75-95% of participants achieved hSBA titres  $\geq 1:4$ , for the three antigens examined (fHbp, NadA and PorA P1.4). Persistence of effect varied depending on the antigen, but the variation was less than that observed in infant vaccinees. Persistence of effect was not tested for antigen NHBA.

#### Persistence 18-23 months post vaccination in adolescents – Study V72P10E1



#### Herd immunity/reduction of carriage:

Study V72\_29 assessed the effect of 4CMenB (2 doses) on the reduction in nasopharyngeal carriage (of all meningococcal B strains (virulent and non-virulent) and all meningococcal ABCWY strains) in university students. Differences at baseline (visit 1), at 1 month after 2<sup>nd</sup> dose (visit 3), and 3 to 11 months after 2<sup>nd</sup> dose (visit 4-6) were reported. There was no statistically significant difference in nasopharyngeal carriage prevalence of virulent strains of meningococcal B in the modified intention to treat (MITT) population. The PBAC considered that the prevalence of virulent strains of meningococcal B was most informative for decision making and noted that ATAGI considered it reasonable to apply a lower value than proposed as the base case efficacy value for reduction of nasopharyngeal carriage in the economic evaluation. The PBAC noted the low absolute value of carriage in the study. The PBAC also noted that the assumption of this analysis is that nasopharyngeal carriage is a surrogate marker for the reduction of transmission of a meningococcal B infection, which can lead to IMD, and the committee considered that it would be difficult to measure herd immunity in terms of reduced IMD in non-vaccinated individuals due to a meningococcal B vaccination program as a) IMD is rare, and b) it would require conducting a large cluster-randomised study in closed environments.

#### Comparative harms

**Infants:** In Studies V72P12 and V72P13, the PBAC noted that adverse reactions were not considered severe, and in line with the minor reactions associated with vaccination.

In both studies, fever ( $\geq 38.0^{\circ}\text{C}$ ) was reported for 41% to 62% of participants after receiving the 4CMenB vaccine concomitantly with routine vaccines, compared with 17% to 36% after routine vaccinations only. In both studies, the occurrence of medically attended fever ranged from 1% to 3% per visit. Both the TGA and ATAGI noted the concerns associated with high rates of fever seen in the 4CMenB + routine vaccinations group, likely due to pyrogens in 4CMenB.

The PBAC agreed with the Economic Sub-Committee (ESC) and the ATAGI advice that prophylactic paracetamol would be appropriate to reduce this high rate of fever because the evidence presented in the Study V72P16 suggested that prophylactic paracetamol did not substantially affect the immune response of concomitant administration of routine vaccines. The PBAC recalled that there is some evidence that paracetamol given after, rather than before, vaccination can reduce the immune response to routine vaccines (Prymula, R et al. Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials, *Lancet*, (2009) 374:1339-1350). However, the ATAGI advice stated 'It is difficult to predict the likely compliance of prophylactic administration of paracetamol to infants who receive other NIP vaccines concurrently with 4CMenB' and 'ATAGI is not confident that a high compliance could be achieved'. The PBAC agreed that uptake and safe compliance of paracetamol was unknown and may be addressed by monitoring of compliance and parent/carer education.

Taking the results of both studies together, 0.7% of participants that received 4CMenB had a febrile seizure, compared to 0.3% of participants that received routine vaccinations only. ATAGI considered that 'it cannot be concluded whether use of 4CMenB in toddlers may increase the risk of febrile seizures' (pre-submission ATAGI advice).

**Adolescents:** The PBAC noted in the trial that less than 5% of the participants across the vaccine groups reported fever ( $\geq 38^{\circ}\text{C}$ ) and there was no difference in the percentage of participants reporting fever between the groups that received 4CMenB and placebo.

## 9. Clinical Claim

The submission described 4CMenB as superior to non-vaccination in terms of comparative effectiveness, with an acceptable tolerability profile in infants and adolescents.

The PBAC agreed 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, the unknown effect upon carriage of the bacteria and the overall uncertain long-term protective efficacy against infection and disease.

## 10. Economic Analysis

The submission presented a modelled economic evaluation (cost utility analysis) based on the claim of superior efficacy and/or safety.

A dynamic transmission model was used to estimate the number of individuals infected with vaccine-preventable meningococci and the number of cases of invasive meningococcal B disease (IMD) that occur. The model consisted of nine mutually-exclusive states, involving a combination of: whether seroprotected; whether infected with vaccine-preventable or non-vaccine-preventable meningococci (or neither); and IMD. All vaccine-preventable strains

have been grouped together, and consequently all transmission and infection parameters are assumed to represent an average across all vaccine-preventable strains.

The submission modelled six vaccination scenarios, representing different combinations of routine infant and adolescent vaccination with or without catch-up programmes:

1. routine infant schedule (four doses at 2, 4, 6 and 12 months of age);
2. routine adolescent schedule (two doses at 15 years of age);
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); and
6. routine infant and adolescent with catch-up for older infants and toddlers and adolescents.

The PBAC agreed that the submission’s proposed base case, scenario 6, was the most clinically appropriate scenario for decision making.

The submission presented an ICER of between \$45,000 and \$75,000 per quality adjusted life year (QALY) for routine infant and adolescent vaccination with catch-up for older infants and toddlers and adolescents versus no vaccination. This is based on a dynamic transmission model, taking the hSBA outcomes (the trial basis of the efficacy point estimates were not specified), applying a modelling horizon of 100 years, and applying utility weights from several published studies and differential annual discount rates for costs and for health outcomes. The PBAC noted that the ICER/QALY was highly sensitive to the discount rate and reiterated that discounting as outlined in its guidelines with sensitivity analysis is most informative for decision making. The PBAC considered that the economic claim is highly uncertain.

The level of concordance between the strains causing meningococcal disease against which 4CMenB is effective and those in circulation in Australia was measured using the Meningococcal Antigen Typing System (MATS) developed by the sponsor. Isolates (n=373) from IMD cases in all States/Territories (excluding Victoria, and 20 from WA) during the period January 2007 to December 2011 were analysed. Isolates that met a minimum threshold of reactivity (fHbp, NHBA and NadA, quantified by ELISA and relative potency compared to a reference strain) or the presence of PorA P1.4 (genotyping) were deemed to be “covered by 4CMenB”. From these data, an estimated 75.9% (95% CI: 63.3%, 86.9%) of isolates would be covered by bactericidal antibody responses to 4CMenB vaccine. The PBAC noted that MATS predicts killing by pooled sera from vaccines shortly after full vaccination. While there is some data to correlate MATS predicted killing with strain coverage, there is no data to confirm correlation between MATS estimated coverage with actual vaccine efficacy. The PBAC noted that MATS provides no information on the proportion of vaccinees who fail to achieve protective titres. The PBAC noted, notwithstanding the technical issues of measuring the NadA coverage with MATS and that seroresponse against two or more antigens would provide a greater degree of certainty of coverage, that the immune response was most robust against NadA, which had the lowest individual coverage.

	Coverage (%) of individual antigen by MATS (Figure C.2.2 of submission)	% participants with bactericidal titres $\geq 1:5$ ‘24m persistence’, Figure 1 (Study V72P13E2)
fHbp	48.0%	62%
NHBA	57.1%	40%

NadA	0.5%	97%
PorA	22.3%	17%

The MATS estimate of coverage might be a reasonable surrogate for clinical efficacy when all vaccinees achieve a protective response against all antigens, but predicting efficacy based on MATS estimated coverage becomes increasingly uncertain if antibody responses are heterogeneous and as antigen-specific titres wane over time. This factor added to the uncertainty of extrapolating vaccine efficacy from the immunogenicity and MATS coverage data.

The submission presented persistence data from V72P13E2, V72P12E1, V72P9E1, V72P6E1 and V72P10E1. The submission assumed that waning follows an exponential curve: an individual is sero-protected against a strain at time 't' if the predicted antibody titre against any of the four antigens expressed by that strain at time t remains above the bactericidal threshold. The PBAC noted that the method for estimating the mean duration of protection against each antigen remained unclear and that the estimates may be inaccurate because of the limited follow-up time in the trials and the uncertain correlation between immunological surrogate and protection.

The model used a 100-year time horizon. The PBAC noted that, with this time horizon and the annual discount rate for outcomes, the model: 1) favours the vaccine in capturing herd effects; and 2) is sensitive both to changes in serotype prevalence over time and also to improvements in management/ decreased morbidity (from disease and sequelae) over time.

The submission's base case economic model assumed a value of 50% for vaccine efficacy on carriage acquisition - the midpoint between a subgroup analysis of carriage study V72\_29 and Maiden & Stuart (2002). Maiden & Stuart (2002) was an observational study examining meningococcal C conjugate vaccination which found a 66% overall reduction in meningococcal C carriage in young adults. Both ESC and ATAGI considered that it was inappropriate to extrapolate data regarding meningococcal C conjugate vaccines to 4CMenB. Both committees considered the data insufficient to support certainty in prediction of herd effects of immunisation in economic analyses and whether the impact on carriage in young adults is applicable to infants. The PBAC agreed with these committees that the claim of the size of the herd immunity effect was highly uncertain, based on the data provided. The sponsor noted the ESC and ATAGI advice and, in the pre-PBAC response, reduced the value for carriage acquisition in the model, the point value of efficacy, 3-11 months after the 2nd dose in the V72\_29 study. The sponsor also offered a price reduction.

The assessment of the vaccine's effect on quality of life was based on utility values for the long-term sequelae taken from several published studies. The PBAC noted that most sources of the utility values and other model inputs were provided before the PBAC meeting. The PBAC noted that no disutilities were applied for adverse events. The PBAC noted that ESC considered it is appropriate not to apply disutilities for febrile events, assuming that prophylactic use of paracetamol is effective, but considered that this assumes that adherence to this recommendation would be high. As paracetamol does not prevent febrile convulsions, the PBAC considered that these adverse events should be included as febrile seizure can lead to long-term sequelae.

The PBAC noted that the estimates in the model for vaccine efficacy before completion of primary infant 3-dose course were 0.42 and 0.61 after one and two doses, respectively. These

values were based on little or no data and the method of calculating the estimates from data on the 4 antigens was not presented.

The PBAC noted that individuals who are sero-protected without vaccination (ie natural immunity) could not enter the sero-protected state. The PBAC considered that it was likely that pre-vaccination sero-protection was not taken into account and that this was not appropriate. The PBAC noted that at least 30-45% of adolescents in the Study V72P10 (conducted in Chile) were already sero-protected at baseline (80-96% against NHBA-containing strains), but they would only enter the sero-protective state following vaccination, which favours the vaccine. The PBAC noted that, in a recent study in the UK, the baseline sero-protection levels in young children (40-44 months of age) were reported as 63% (46-77) for fHpb, 3% (0-13) for NadA, and 0% (0-9) for PorA (Snape, 2013). The PBAC noted in the ATAGI advice that only a small proportion of Australian adolescents (aged 11–17 years) who participated in a study had baseline bactericidal titre of  $\geq 1:5$  against the indicator strains (7%, 1% and 0% against, fHbp and NadA, PorA respectively). baseline levels varied by antigen, by age (infants vs adolescents) and by geographic region. The PBAC considered additional data on natural immunity to the antigens of 4CMenB in Australia would be informative to the economic evaluation.

The PBAC noted that changing the assumptions from those originally submitted in the economic model to those in the pre-PBAC response resulted in minor changes to the ICER/QALY. However, when recalculated with annual discount rates of 5.0% costs/5.0% outcomes, the ICER for the base case Scenario 6 was greater than \$200,000/QALYG.

The PBAC noted from sensitivity analyses of discounting and price, using the pre-PBAC response model, that a further price reduction would be necessary to give an ICER/QALY in the range that the PBAC has accepted for other vaccines it has recommended for inclusion in the NIP.

## 11. Estimated PBS Usage and Financial Implications

The submission estimated that over 4 million children and adolescents would be vaccinated over the first 5 years of a full vaccination program.

The PBAC noted the crude estimates provided by ATAGI of the number of invasive meningococcal B disease (IMD) cases, deaths and sequelae that could potentially be prevented through implementation of a 4CMenB immunisation program. These are presented in the table below. The PBAC noted that the estimates were based on the following assumptions: diagnosis of meningococcal B in 2006-2011, indirect herd protection effect was not taken into account, no waning of vaccine effectiveness would occur in the first 5 years, vaccine efficacy and strain coverage were based on the results of a number of clinical studies, vaccine uptake (coverage) assumptions were based on previous experience of similar vaccine schedules in Australia.

Age group	Cumulative total after first 5 years of program			Cumulative total after first 10 years of program		
	Number of MenB IMD cases prevented	Number of MenB IMD deaths prevented	Number of patients with sequelae prevented	Number of MenB IMD cases prevented	Number of MenB IMD deaths prevented	Number of patients with sequelae prevented
<1 year	92	5	31	184	9	63
<5 years (incl <1yr)	154	7	53	370	16	128

15–24 years	70	2	39	211	6	119
<b>Total for all ages</b>	<b>224</b>	<b>9</b>	<b>93</b>	<b>591</b>	<b>22</b>	<b>250</b>

MenB: meningococcal B; IMD: invasive meningococcal B disease

The cumulative cost of the programme over 5 years was estimated to be greater than \$400 million.

The PBAC noted that cost of implementing the programme in school may be underestimated. The sponsor assumed that the implementation of 4CMenB in schools would add approximately 1.0% to the overall cost of the vaccinations received at school, while a likely cost could be around 15.5% of the vaccination costs for adolescents, based on the 2004 report from the Municipal Council of Victoria.

## 12. Recommendation and Reasons

The PBAC did not recommend the inclusion of the 4CMenB vaccine on the National Immunisation Program Schedule for the prevention of meningococcal B disease in infants and adolescents.

The PBAC considered the burden of meningococcal disease, the public concern about rapidly developing and often fatal infection, and that the development of the proposed vaccine may represent a technical advance in the field of vaccinology. The PBAC concluded that, over the first 5 years of the requested NIP listing as proposed by the sponsor: over 4 million children and adolescents would be vaccinated costing the government over \$400 million, estimated to prevent 224 cases of invasive meningococcal disease, 9 deaths due to meningococcal B disease, and 93 patients with sequelae. However, the PBAC considered that 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 unacceptability high and was based on uncertain assumptions about extent and duration of effect and herd immunity.

The PBAC noted that the reverse vaccinology employed in the development of the 4CMenB vaccine overcame the considerable block to the development of a vaccine against meningococcal B strains where, unlike non-strain B meningococcal strains, the polysaccharide capsule from the bacterial cell wall is poorly immunogenic and has a structure similar to polysaccharides in the developing human central nervous system.

The PBAC noted the rapid onset of disease following infection and that clinical improvement in diagnosis and management of the infection has had little impact on IMD outcomes. The PBAC noted the strong consumer support for this submission, highlighting the community's desire to overcome IMD.

The PBAC noted that there are a number of aspects of the clinical data that leads to an uncertain claim of clinical effectiveness.

Firstly, the PBAC noted that no direct evidence was presented regarding vaccine efficacy against infection and disease. Due to the low infection rates of meningococcal B, a randomised efficacy study is not feasible. The PBAC accepted that hSBA titre threshold of  $\geq 1:4$  is historically a 'gold standard' surrogate marker of vaccine efficacy, and this titre was accepted in the consideration of the combination vaccine for *Haemophilus influenzae* and *Neisseria meningitis* serogroup C. The PBAC noted that the threshold titre value was

determined based on the polysaccharide capsule, not bacterial proteins, as used in the 4CMenB, and considered that the validity of this surrogate outcome and threshold titre of adequate protection had not been addressed in relation to the structure of the components of the proposed vaccine.

Secondly, the PBAC accepted that the data showed a clear immunogenic effect of the vaccine, but considered that the long-term persistence of a protective immune response had not been adequately supported. In the trials of infant vaccinees, antibody titres waned quickly and at different rates, particularly titres against PorA P1.4 and NHBA.

Thirdly, the PBAC considered that ability of the vaccine to generate a protective herd immune response on a population level had not been demonstrated. The PBAC considered that carriage should be estimated based on the evidence on virulent meningococcal B strains, but not other non-B meningococcal strains. The PBAC considered it was not reasonable to use data from a carriage study of a meningococcal C conjugate vaccine (Maiden & Stuart, 2002) to estimate the reduction of carriage acquisition, given the differences of bacterial strains and vaccine components (polysaccharide vs protein). The PBAC accepted the ATAGI advice of the vaccine's efficacy against nasopharyngeal carriage, based on the V72\_29 study. The PBAC considered that there is insufficient evidence to accept that the carriage study presented in the submission (of 1,958 university students, (150 individuals with virulent meningococcal B)) is applicable to infants. The PBAC noted in a recent publication of another vaccine against meningococcal B (Delbos V et al, Impact of MenBvac, an outer membrane vesicle (OMV) vaccine, on the meningococcal carriage, 2013, Vaccine, 31:4416-20) that, during a meningococcal B outbreak, the carriage rate was 1.2% (9 confirmed meningococcal B in 761 unvaccinated children, aged 1-7).

Fourthly, the PBAC noted that the submission estimated that 75.9% (95% CI: 63.3%, 86.9%) of clinical isolates would be covered by bactericidal antibody responses elicited by 4CMenB, using the MATS. The PBAC was concerned that this typing system was an *in vitro* method and that the basis of the claim that MATS is a correlate of protection is not clear. The PBAC noted that assay was carried out on pooled immune sera of infants taken 1 month after the 4<sup>th</sup> dose of 4CMenB, at the likely peak of the antibody response. The PBAC agreed that the MATS estimate of coverage might be a reasonable surrogate for clinical efficacy when all vaccinees achieve a protective response against all antigens, but the committee considered that predicting efficacy based on MATS estimated coverage becomes increasingly uncertain if individual antibody responses are heterogeneous and as antigen-specific titres wane over time. The PBAC, noting that 36.7% (upper bound of the 95% CI) of meningococcal B strains may not be covered by the vaccine, considered that monitoring of long-term variation of meningococcal B strains in the community was an important issue to be addressed in any implementation of a vaccine programme.

The PBAC accepted in general that the local transient reactogenicity of 4CMenB was not different to routine vaccination. The PBAC noted the rates of fever in infant participants of the trials receiving 4CMenB and agreed with the ATAGI that prophylactic paracetamol would be appropriate, as the evidence presented in the submission suggested that prophylactic paracetamol did not substantially affect the immune response of concomitant administration of routine vaccines. The PBAC recalled that prophylactic paracetamol was recommended with the use of the diphtheria-tetanus-whole cell pertussis vaccine (DTPw), before the acellular vaccine was introduced on the NIP. The PBAC noted that ATAGI was unable to identify reliable data or studies on compliance with the recommendation for

prophylactic use of paracetamol. The PBAC agreed with ATAGI that it is difficult to predict the likely compliance of prophylactic paracetamol. Given that paracetamol does not prevent febrile convulsions, the PBAC considered that parent/carer education, surveillance of the use of paracetamol and of emergency department admissions for febrile convulsions were important issues to be addressed in any implementation of a vaccine programme. This would help minimise the risk of reduced coverage rates for infant vaccination overall due to loss of confidence in immunisation arising from concerns about increased rates of fever and convulsions.

The PBAC considered that, given its questions about the clinical efficacy of 4CMenB, the economic evaluation was highly uncertain due to the assumptions used in the model and the proposed price of the vaccine.

The PBAC noted that the estimates in the model for vaccine efficacy before completion of primary infant 3-dose course were 0.42 and 0.61 after one and two doses, respectively. The source of these estimates was not presented in the submission, but the PBAC accepted the advice from ATAGI that considered the estimate of 0.61 was reasonable and the estimate of 0.42 was reasonable but imprecise.

The PBAC accepted the time horizon of 100 years used in the model, in line with other vaccines considered by the PBAC. However, the committee considered that it was not reasonable to assume that, over 100 years, the distribution of strains would not change, that each case would result in the same reduction in quality of life and there would be no improvement in the outcomes of meningococcal disease or in the management of disabilities over this time frame.

The PBAC noted that, in the economic model, individuals who had natural immunity could not enter the sero-protected state, only vaccinated individuals. The PBAC considered that this assumption favoured the vaccine, particularly in the adolescent cohort. The PBAC noted that there was limited data available on the levels of natural immunity to meningococcal B strains in Australia to inform this assumption of the economic model.

The PBAC noted that the submission presented the base case of the economic evaluation with a differential annual discount rate for costs and for outcomes. The ICER/QALY was highly sensitive to the discount rates applied to costs and outcomes. The PBAC considered that, consistent with its consideration of other vaccines for the NIP, it was not reasonable to apply differential discount rates in the base case of the economic model. The PBAC noted the discussion by ESC about discounting rates in economic modelling. The sponsor argued that the application of differential discounting to the economic model was appropriate because ‘the burden mainly occurs at an early age implying the loss of many decades of life and early incident of permanent disability that lasts for the rest of life. In addition, a specific benefit of intervention with 4CMenB, as opposed to non-vaccine interventions, is that there is a disproportionate benefit accumulated over time, as the proportion of the population who are protected increases (herd effect).’ The PBAC did not accept this argument as the long-term efficacy of the vaccine in individuals and the reduction of carriage has not been adequately demonstrated in the submission. 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). The PBAC considered

that NIP listing should only occur at a price that produces an acceptable ICER as a basis for PBAC recommendation.

The PBAC considered that it was not informative to consider a hyperendemic scenario in the economic evaluation for the inclusion of 4CMenB in the NIP, noting that the predictability of a hyperendemic scenario is such that it does not inform routine decision making. The PBAC noted that hyperendemic meningococcal B outbreaks had occurred in New Zealand but did not consider that similar outbreaks were necessarily likely to occur in Australia.

The PBAC noted that there is a higher IMD burden in the Aboriginal and Torres Strait Islander (ATSI) 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 did not consider it appropriate to recommend NIP listing of 4CMenB for use in the ATSI population only given the uncertain clinical efficacy and unacceptable cost-effectiveness of the vaccine. The PBAC also noted the concerns of ATAGI that targeted immunization strategies in this population have achieved suboptimal vaccine coverage compared to universal strategies, that benefits would be realized on an individual not group basis, and that there would be considerable implementation and communication issues to consider around perceived differences in the risk-benefit acceptability of the vaccine for Indigenous versus non-Indigenous populations.

The PBAC noted the successful introduction of the meningococcal C conjugate vaccine into Australia. Confirmed cases of IMD caused by meningococcal C have fallen to almost zero within 10 years of introduction of this conjugate vaccine. The PBAC also noted the recent success in decreasing the incidence of meningococcal disease by a vaccine against the meningococcal A strain in Africa.

The PBAC noted that, in the financial estimates section of the submission, the sponsor estimated over 4 million children would be vaccinated over the first 5 years of a full 4CMenB vaccination programme (including catch ups), at a net cost to the government of greater than \$400 million. Based on estimates provided by ATAGI, this vaccination programme would prevent 224 cases of invasive meningococcal disease, 9 deaths due to meningococcal B disease, and 93 patients with sequelae after 5 years. The PBAC concluded that the rarity of invasive meningococcal B disease compared to the large number of vaccinations that are required was the primary driver of the unfavourable incremental cost-effectiveness ratio. The PBAC considered that, given the clinical uncertainties of a population wide prevention, there was high financial risk to the government and reduced opportunity to fund other interventions which are acceptably cost-effective.

The PBAC noted the sponsor's proposal to support additional research to address and potentially manage uncertainties associated with implementing the requested NIP listing:

- continuation of the MATS analysis;
- an effectiveness study, similar to the observational study protocol (Study V72\_38OB) developed with Public Health England, which uses a screening method. Uptake and routine surveillance data for meningococcal disease would allow assessment of the vaccine effectiveness, as well as help provide longer-term answers on geographical strain coverage (by incorporating data from MATS), waning, herd immunity and capsule replacement;
- a vaccine registry;

- a carriage study, such as a school-based study comparing carriage at baseline and after introduction of the vaccine in a national programme. The study's scope, protocol, choice of investigators and governance could be defined and agreed upon in further discussions with ATAGI.

The PBAC agreed that this research could provide valuable information to address many of the clinical issues raised during the committee's consideration of the submission.

The PBAC noted that a registry would need to cover an age range of 2 months to early adulthood. In Australia there are two national vaccine registries: the Australian Childhood Immunisation Register (ACIR, up to the age of 7) and the National HPV Vaccination Program Register (adolescents to early adulthood). The PBAC considered the expansion of the ACIR to monitor immunisation coverage levels for the whole of life would be preferable option over the creation of a third registry.

The PBAC noted that a controlled intervention study in the Oxford Health region of a Hib conjugate vaccine was completed in 1991 to address concerns of adding Hib conjugate vaccines to the UK national immunisation programme. Routine immunisation with Hib conjugate was introduced in October 1992 in the UK, resulting in near elimination of Hib disease (review by Heath & McVernon (Heath, PT & McVernon, J. The UK Hib vaccine experience. Arch Dis Child, 2002: 86:396-99)). The PBAC advised that consideration should be given to conducting a cluster randomised controlled trial (possibly clustering at State and Territory level) as a robust method of addressing uncertainties of the clinical effectiveness of the vaccine. If feasible, the PBAC considered that such a trial should be included as a component of the sponsor-supported additional research.

The PBAC considered whether a managed entry approach would be appropriate for the 4CMenB vaccine to accommodate these research proposals. Co-implementation with the sponsor of such a scheme would likely address the extent and persistence of vaccine effectiveness, the extent of the reduction of nasopharyngeal carriage leading to extent of herd immunity, the surveillance for reactogenicity and the requirement of an additional booster dose at age of 4 or in early adulthood.

However, the PBAC held grave concerns that if NIP listing was implemented in the context of a managed entry scheme, and the research subsequently showed that the expected benefits were not realised, there would be great difficulty associated with disinvestment and removal of the vaccine from the NIP, and such an event may undermine public confidence in immunisation in general.

***Recommendation:***

Rejected

**13. 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.

## 14. Sponsor's Comment

Novartis is disappointed by the decision of the PBAC not to recommend Bexsero<sup>®</sup> for inclusion onto the National Immunisation Programme (NIP) at this time. Meningococcal B is the single leading cause of bacterial meningitis and sepsis in Australian infants and teenagers, accounting for approximately 85% of all meningococcal disease cases. The disease is easily misdiagnosed in its early stages and can develop rapidly, frequently leading to death or permanent disability within 24 hours of onset of symptoms.

Novartis is committed to the inclusion of Bexsero<sup>®</sup> on the NIP, since we believe that widespread use of the vaccine will significantly reduce the risk of this devastating disease in the Australian community. Novartis has carefully considered the PBAC's commentary on the submission and is working with the Committee to address all outstanding areas of uncertainty in a resubmission to the PBAC submitted March 2014.

## ADDENDUM - JULY 2014

### 7.4 MULTICOMPONENT MENINGOCOCCAL GROUP B VACCINE (4CMenB), injection, 0.5mL, Bexsero, Novartis Vaccines and Diagnostics Pty Ltd.

#### 1 Purpose of Application

- 1.1 To request the inclusion of a four component meningococcal B (4CMenB) vaccine on the National Immunisation Program (NIP) Schedule for prevention of meningococcal B disease in infants and adolescents. The PBAC previously considered the 4CMenB vaccine at the November 2013 meeting.

#### 2 Requested listing

- 2.1 The resubmission requested inclusion of the 4CMenB vaccine in the NIP with the proposed vaccination schedule as presented in the table below. This was unchanged from the previous submission.

Proposed Australian NIP Dosage Schedule by age for 4CMenB vaccine

Target age/age-group (at first dose)	No. of primary doses	Schedule proposed	Booster dose requirement (age)
<b>A) Routine vaccination program</b>			
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>B) Catch-up vaccination program†</b>			
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.

† Catch-up vaccination program is assumed to be implemented in the first year of implementation.

Source: Table A.2.2, pA-32 of the resubmission.

#### Proposed NIP listing details

Form & strength	Max. qty	No. of repeats	Proprietary name and manufacturer	
Meningococcal group B ( <i>Neisseria meningitidis</i> ) vaccine, 1 x 0.5 mL syringe	1	0	Bexsero	Novartis Vaccines & Diagnostics
Meningococcal group B ( <i>Neisseria meningitidis</i> ) vaccine, 10 x 0.5 mL syringes	1	0	Bexsero	Novartis Vaccines & Diagnostics

2.2 Listing was sought on a cost-effectiveness basis of the vaccine compared to no vaccination.

### 3 Background

3.1 Meningococcal group B vaccine was TGA registered on 14 August 2013 for active immunisation against invasive disease caused by *Neisseria meningitidis* group B strains.

3.2 This was the second consideration by the PBAC.

#### Summary of differences between the previous submission and current resubmission

	4CMenB, November 2013		Current resubmission
	Submission	Considered at PBAC meeting	
Requested price	\$█ per dose, plus █% discount in the catch-up program.	\$█ per dose.	\$█ per dose, plus █% discount in the catch-up program.
Economic evaluation	Cost-utility model with an ICER of \$█/QALY for routine infant and adolescent vaccination with catch-up for older infants and toddlers and adolescents versus no vaccination.	Cost-utility model with an ICER of \$█/QALY for routine infant and adolescent vaccination with catch-up for older infants and toddlers and adolescents versus no vaccination. <b>PBAC comment:</b> the PBAC preferred model had an ICER of \$█/QALY (item 6.37).	Cost-utility model with an ICER of \$█/QALY in the base case for routine infant and adolescent vaccination with catch-up for older infants and toddlers and adolescents versus no vaccination.
	The submission's 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% per annum for costs and █% per annum for health outcomes, a █% for vaccine impact on carriage acquisition (herd immunity response), and \$█/dose.	A revised base case was presented, with differential annual discount rates of 5% per annum for costs and █% per annum for health outcomes, a █% for vaccine impact on carriage acquisition (herd immunity response), and \$█/dose. <b>PBAC comment:</b> the PBAC preferred model was based on the above but with non-differential annual discount rates of 5% for costs and health outcomes (item 6.37).	A revised base case was presented, with non-differential annual discount rates of 5% per annum for costs and health outcomes (plus sensitivity analysis). Additionally vaccine coverage, projected births, deaths, and life expectancy were updated, and costs inflated using the CPI.  Furthermore the resubmission presents only one scenario (Scenario 6 - infants and adolescents routine vaccination plus catch-up programs), and explains the calculation of vaccine efficacy and persistence.

Number of patients	4,704,555 individuals vaccinated over 5 years.	<b>PBAC comment:</b> none.	4,861,730 individuals vaccinated over 5 years.
Estimated cost to the NIP	\$ [REDACTED] over the first 5 years of listing.	\$ [REDACTED] over the first 5 years of listing. <b>PBAC comment:</b> none.	\$ [REDACTED] over the first 5 years of listing.
Risk-share scheme	A [REDACTED] % price reduction for 4CMenB under the catch-up programs for children and adolescents. Plus continuation of MATS analysis.	A [REDACTED] % 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 'free of charge' booster dose (at age 4 or 21), 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 results of the observational study V72_38OB (using screening methods) be provided to ATAGI, or a similar study be conducted in Australia.	A [REDACTED] % 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 covering both age categories 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 - a safety study using regular passive, enhanced and active pharmacovigilance. Plus a 'free of charge' booster dose (at age 4 or 21), if necessary.

CPI = consumer price index; hSBA = human Serum Bactericidal Assay; ICER = incremental cost-effectiveness ratio; IMD = invasive meningococcal B disease; MATS = Meningococcal Antigen Typing System; QALY = quality adjusted life year.  
Source: Table 3, p3 of the commentary.

#### 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).

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

#### 5 Comparator

- 5.1 The comparator was no vaccination. This was unchanged from the previous submission.

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

## 6 Consideration of the evidence

### *Sponsor hearing*

6.1 There was no hearing for this item.

### *Consumer comments*

6.2 The PBAC noted and welcomed the input from individuals (40), health care professionals (3) and organisations (6) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with 4CMenB including preventing death and significant disability from the sudden onset of invasive meningococcal B disease.

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

### *Clinical trials*

6.3 The clinical trials listed below were unchanged from the previous submission.

Trial ID	Protocol title/ Publication title	Publication citation
<b>Infant studies</b>		
V72P12	<p>A Phase 2b, Open Label, Randomized, Parallel-Group, Multicenter Study to Evaluate the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine When Administered with or without Routine Infant Vaccinations to Healthy Infants According to Different Immunization Schedules. September 2010. Clinical Study Report: V72P12. Novartis Vaccines and Diagnostics. (Pollard A et al. 2010)</p> <p>AND</p> <p>████████████████████</p> <p>Gossger N, Snape MD, Finn A et al. Immunogenicity of an investigational multicomponent meningococcal serogroup B vaccine (4CMenB) administered with or without routine infant vaccinations in different schedules.</p> <p>Gossger, N., Snape, M. D., et al. (2012). Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: A randomized controlled trial.</p> <p>Cohn, A. C. and Messonnier, N. E. (2012). Inching toward a serogroup B meningococcal vaccine for infants.</p> <p>Vesikari, T., S. Esposito, et al. (2013). Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: Results of two randomised trials.</p> <p>Beeretz I, Snape MD, Finn A et al. Reactogenicity and safety of multicomponent meningococcal serogroup B vaccine (4CMenB) administered with or without routine infant vaccinations in different schedules.</p>	<p>2010</p> <p>Poster presented at 29th ESPID Meeting, 7-11 June 2011, The Hague, The Netherlands.</p> <p>JAMA - Journal of the American Medical Association 307(6): 573-582</p> <p>JAMA - Journal of the American Medical Association 307(6): 614-615.</p> <p>The Lancet 381(9869): 825-835.</p> <p>Poster No. 1187. Presented at 29th ESPID Meeting, 7-11 June 2011, The Hague, The Netherlands.</p>
V72P12E1	A Phase 2b, Open Label, Multi-Center, Extension Study to Evaluate the Safety, Tolerability and Immunogenicity of a Booster Dose of	November 2012

	<p>Novartis Meningococcal B Recombinant Vaccine Administered at 12, 18 or 24 Months of Age in Participants Who Previously Received a Three-Dose Primary Series of the Novartis Meningococcal B Recombinant Vaccine as Infants in Study V72P12. November 2012. Clinical Study Report V72P12E1 Novartis Vaccines and Diagnostics.</p> <p>Snape, MD, Finn A, Heath et al. Persistence to 12, 18 and 24 months of bactericidal antibodies induced by infant immunisation with a serogroup B meningococcal vaccine.</p>	<p>Poster presented at 31st ESPID Meeting, May 28-June 1 2013, Milan, Italy.</p>
V72P13	<p>A Phase 3, Partially Blinded, Randomized, Multicenter, Controlled Study to Evaluate Immunogenicity, Safety and Lot to Lot Consistency of Novartis Meningococcal B Recombinant Vaccine When Administered with Routine Infant Vaccinations to Healthy Infants. September 2010. Clinical Study Report: V72P13. Novartis Vaccines and Diagnostics.</p> <p>AND</p> <p>████████████████████</p> <p>Vesikari, T., Esposito, S., et al. (2010). Immunogenicity of an investigational multicomponent meningococcal serogroup B vaccine in healthy infants at 2, 4 and 6 months of age.</p> <p>Vesikari, T., Esposito, S., et al. (2011). Use of an investigational multicomponent meningococcal serogroup B vaccine (4cmenb) in a clinical trial in 3630 infants.</p> <p>Vesikari, T., S. Esposito, et al. (2013). Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: Results of two randomised trials.</p>	<p>September 2010</p> <p>Canadian Journal of Infectious Diseases and Medical Microbiology 21(4): 183</p> <p>Archives of Disease in Childhood 96: A3.</p> <p>The Lancet 381(9869): 825-835.</p>
V72P13E1	<p>A Phase 3, Open label, Multi-Center, Extension Study to Evaluate the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine When Administered as a Booster at 12 Months of Age or as a Two-dose Catch-up to Healthy Toddlers Who Participated in Study V72P13. November 2010. Clinical Study Report: V72P13E1. Novartis Vaccines and Diagnostics.</p> <p>AND</p> <p>████████████████████</p> <p>Vesikari T, Prymula R, Liese J et al. Booster dose at 12 months of an investigational meningococcal serogroup B vaccine (4CMenB) in healthy toddlers previously primed at 2,4,6 months.</p> <p>Prymula R, Vesikari T, Esposito S, et al. Catch-up vaccination of healthy toddlers with an investigational meningococcal serogroup B vaccine (4CMenB) - exploration of a two-dose schedule.</p> <p>Toneatto D, Prymula R, Merrall E et al. Immunogenicity and reactogenicity of two-dose vaccination with investigational meningococcal b recombinant vaccine at 24 and 26 months of age.</p>	<p>November 2010</p> <p>Poster presented at 29th ESPID Meeting, 7-11 June 2011, The Hague, The Netherlands.</p> <p>Poster presented at 29th ESPID Meeting, 7-11 June 2011, The Hague, The Netherlands.</p> <p>Poster presented at 31st ESPID Meeting, May 28-June 1 2013, Milan, Italy.</p>
V72P13E2	<p>A Phase 3, Open label, Multi-Center, Extension Study of V72P13E1 to Assess Antibody Persistence at One Year After a Fourth Dose Boost or Two Catch-Up Doses of Novartis Meningococcal B Recombinant Vaccine Administered Starting at 12 Months of Age and to Evaluate the Response to a Third Dose Boost or Two Catch-Up Doses Starting at 24 Months of Age. May 2012. Clinical Study Report: V72P13E2. Novartis Vaccines and Diagnostics</p>	<p>May 2012</p>

<b>Supplementary infant studies presented in Section C</b>		
V72P6	A Phase 2, Open Label, Multi-Center, Controlled, Randomized Study of the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine±OMV, when Administered to Healthy Infants at 2, 4, 6 and/or 12 Months of Age. Clinical Study Report: V72P6. Novartis Vaccines and Diagnostics	April 2009
V72P6E1	Snape MD, Saroey P, John TM, Robinson H, Kelly S, Gossger N, Yu LM, Wang H, Toneatto D, Dull PM, Pollard AJ. (2013) Persistence of bactericidal antibodies following early infant vaccination with a serogroup B meningococcal vaccine and immunogenicity of a preschool booster dose.	CMAJ. 185(15):E715-24.
V72P9	A Phase 2, Single Blind, Single Center, Randomized Study of the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine ± OMV, when Administered to Healthy Infants 6-8 months old. Clinical Study Report: V72P9. Novartis Vaccines and Diagnostics	February 2009
V72P9E1	<p>A Phase 2, Open-Label, Single-Center, Extension Study Evaluating Antibody Persistence compared to Naive Children and Safety, Tolerability and Immunogenicity of a Booster Dose of Novartis rMenB±OMV NZ Vaccine in Healthy UK Children Who Previously Received a Three-Dose Series of the Novartis Vaccine as Infants in Study V72P9. Clinical Study Report: V72P9E1. Novartis Vaccines and Diagnostics</p> <p>Philip J, Snape MD, Robinson H, Kelly S, Pollard AJ, John TM, Gossger N, Toneatto D, Kittel C, Kimura A, Dull PM. (2012) Bactericidal antibody persistence two years following meningococcal B vaccination at 6, 8 and 12 months in 40 month old children</p> <p>Snape MD, John TM, Kelly S, Robinson H, Houlden J, Toneatto D, Kittel C, Dull PM, Pollard AJ. (2013) Persistence of bactericidal antibodies to 5 years of age following a 'preschool' booster dose of serogroup B meningococcal vaccine</p> <p>Snape MD, Philip J, John TM, Robinson H, Kelly S, Gossger N, Yu LM, Kittel C, Toneatto D, Dull PM, Pollard AJ. (2013) Bactericidal antibody persistence 2 years after immunization with 2 investigational serogroup B meningococcal vaccines at 6, 8 and 12 months and immunogenicity of preschool booster doses: a follow-on study to a randomized clinical trial.</p>	<p>December 2011</p> <p>Poster presented at 30th ESPID Meeting, May 8-12 2012, Thessaloniki, Greece.</p> <p>Poster presented at 31st ESPID Meeting, May 28-June 1 2013, Milan, Italy.</p> <p>Pediatr Infect Dis J. 32(10):1116-21.</p>
<b>Adolescent studies</b>		
V72P10	<p>A Phase 2b/3, Multi-Center, Observer-Blind, Controlled Study of the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine Administered to Healthy Adolescents Aged 11-17 Years According to Different Vaccination Schedules. June 2011. Clinical Study Report: V72P10. Novartis Vaccines and Diagnostics. (Santolaya et al. 2011a)</p> <p>AND</p> <p>██████████</p> <p>Santolaya, M. E., O'Ryan, M. L., et al. (2012). Immunogenicity and tolerability of a multicomponent meningococcal serogroup B (4CMenB) vaccine in healthy adolescents in Chile: A phase 2b/3 randomised, observer-blind, placebo-controlled study.</p> <p>Stephens, D. S. (2012). Prevention of serogroup B meningococcal disease.</p>	<p>June 2011</p> <p>The Lancet 379(9816): 617-624.</p> <p>The Lancet 379(9816): 592-594.</p>
V72P10E1	A Phase 2b/3, Multi-Center, Extension Study of V72P10 to Assess Antibody Persistence at Eighteen Months After the Completion of the Vaccination Course in Study V72P10. October 2012. Clinical Study	October 2012

	<p>Report V72P10E1. Novartis Vaccines and Diagnostics.</p> <p>Santolaya ME, O’Ryan MO, Valenzuela MT et al. Persistence of antibodies 18–24 months after adolescent immunization with 1–3 doses of a multicomponent meningococcal serogroup B vaccine.</p> <p>Santolaya ME, O’Ryan M, Dull, P. et. al. Persistence of antibodies in adolescents 18–24 mo after immunization with one, two or three doses of 4CMenB meningococcal serogroup B vaccine.</p> <p>Santolaya, M. E., O’Ryan, M. L., et al. (2013). "Persistence of antibodies in adolescents 18-24 months after immunization with one, two, or three doses of 4CMenB meningococcal serogroup B vaccine."</p>	<p>Poster presented at 31st ESPID Meeting, May 28-June 1 2013, Milan, Italy.</p> <p>Human Vaccines &amp; Immuno. Vol 9 Issue 11 June 2013 (e-pub ahead of print)  <a href="http://www.landesbioscience.com/journals/vaccines/article/25505/">http://www.landesbioscience.com/journals/vaccines/article/25505/</a></p> <p>Human Vaccines and Immunotherapeutics 9(11): 2304-2310.</p>
<b>Nasopharyngeal carriage study presented in Section C</b>		
V72_29	<p>A Phase 3 Observer blind Randomized, Multi-center, Controlled study to evaluate the effect of Novartis Vaccine’s Meningococcal B recombinant and MenACWY Conjugate vaccines on Pharyngeal Carriage of N. meningitidis in Young Adults. Clinical Study Report V72_29. Novartis Vaccines and Diagnostics.</p> <p>Read, RC. Baxter, D. Chadwick, DR. et al (2013) Impact of a quadrivalent conjugate (MenACWY-CRM) or a serogroup B (4CMenB) meningococcal vaccine on meningococcal carriage in English university students</p>	<p>July 2013</p> <p>Presented at 31st ESPID Meeting, May 28-June 1 2013, Milan, Italy.</p>

Source: Table B.2.3 of the commentary.

### **Comparative effectiveness**

- 6.4 The estimates of comparative benefit were unchanged from the previous submission. The resubmission also presented an ad-hoc sub-group analysis of Studies V72P12 and V72P13 to explore the impact of concomitant administration of a rotavirus vaccine with 4CMenB.
- 6.5 The ESC considered that the additional data provided reassurance that rotavirus vaccination is unlikely to impact on 4CMenB efficacy and vice versa.
- 6.6 In November 2013, the PBAC accepted that hSBA titre threshold of  $\geq 1:4$  is historically a ‘gold standard’ surrogate marker of vaccine efficacy, and this titre was accepted in the consideration of the combination vaccine for *Haemophilus influenzae* and *Neisseria meningitidis serogroup C*. The PBAC noted that the threshold titre value was determined based on the polysaccharide capsule, not bacterial proteins, as used in the 4CMenB, and considered that the validity of this surrogate outcome and threshold titre of adequate protection had not been addressed in relation to the structure of the components of the proposed vaccine. The PBAC accepted that the data showed a clear immunogenic effect of the vaccine, but considered that the long-term persistence of a protective immune response had not been adequately supported. In the trials involving the vaccination of infants, antibody titres waned quickly and at different rates, particularly titres against PorA P1.4 and Neisseria heparin binding antigen (NHBA). The PBAC considered that ability of the vaccine to generate a protective herd immune response at a population level had not been demonstrated.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

## Comparative harms

- 6.7 The estimates of comparative harms were unchanged from the previous submission. The resubmission also presented safety data regarding the recent use of 4CMenB among young adults to address two university-based meningococcal B disease outbreaks in the United States and an updated safety risk management plan.
- 6.8 The ESC noted that safety in adolescents appears to be acceptable and that the safety profile in this age group is superior to the infant population due to the increase in febrile seizures experienced in infants.
- 6.9 The results from the dynamic transmission model, which converted the estimated immunogenicity results from the clinical trials into the number of IMD cases avoided and the number of deaths avoided, were changed from the previous submission. The estimates of harms were unchanged from the previous submission.

### Summary of comparative benefits and harms for 4CMenB versus no vaccination

Benefits							
Trial	4CMenB	No vaccination	Difference	Event rate/100 vaccinations		RD/100 vaccinations	NNT
				4CMenB	No vaccination		
<b>IMD cases (based on dynamic transmission model) *</b>							
Over 100 years	■	■	■	■	■	■	■
Over 5 years	■	■	■	■	■	■	■
<b>Deaths (based on dynamic transmission model) *</b>							
Over 100 years	■	■	■	■	■	■	■
Over 5 years	■	■	■	■	■	■	■
<b>Harms</b>							
Trial	4CMenB + routine vaccinations	Routine vaccinations	RR (95% CI)	Event rate/100 vaccinations **		RD/100 vaccinations	NNH ##
				4CMenB	Placebo		
<b>Fever ≥ 38.5°C in infants</b>							
V72P12	■	■	■	■	■	■	■
V72P13	■	■	■	■	■	■	■
<b>Medically attended fever in infants</b>							
V72P12	■	■	■	■	■	■	■
V72P13	■	■	■	■	■	■	■
<b>Febrile seizure in infants</b>							
V72P12 and V72P13	■	■	■	■	■	■	■
<b>Fever ≥ 38.5°C in adolescents</b>							
V72P10, 1 <sup>st</sup> vaccination	■	■	■	■	■	■	■
V72P10, 2 <sup>nd</sup> vaccination	■	■	■	■	■	■	■

IMD = Invasive meningococcal B disease; NA = not applicable; NR = not reported, RD = risk difference; RR = relative risk.

\* The results from the dynamic transmission model were presented as they are more clinically relevant than the immunogenicity results reported by the clinical trials.

\*\* Maximum duration of exposure: V72P12 and V72P13 = 3 doses (primary vaccination).

# Number needed to vaccinate to avoid one case = 71,934,378 vaccinated / cases or deaths avoided (number vaccinated based on sheet "Vaccine inputs\_str1" in Attach 11\_Economic Model 1.xls).

§ Number needed to vaccinate to avoid one case = 3,538,914 vaccinated / cases or deaths avoided (number vaccinated based on sheet "Vaccine inputs\_str1" in Attach 11\_Economic Model 1.xls).

## Number of vaccinations to cause one AE = 1 / RD.

Source: Table 5 of the commentary.

- 6.10 The PBAC noted that, on the basis of the results of the dynamic infectious disease model presented in the resubmission to translate serologic response reported in the trials:
- approximately 336 IMD cases would be avoided over 5 years and approximately 10,532 individuals would need to be fully vaccinated to avoid one IMD case (over 5 years)
  - approximately 13 deaths would be avoided over 5 years and approximately 272,224 individuals would need to be fully vaccinated to avoid one death (over 5 years).

The PBAC noted that, on the basis of the results of studies V72P12 and V72P13 in infants presented in the resubmission, and thus without effective prophylaxis with paracetamol:

- approximately one fever  $\geq 38.5^{\circ}\text{C}$  would occur in every 4 to 6 vaccinations in infants
- approximately one medically attended fever would occur in every 228 to 588 vaccinations in infants
- approximately one febrile seizure would occur in every 2,500 vaccinations in infants.

The rate of fever in adolescents is much lower.

- 6.11 The PBAC recalled that in consideration of submission in November 2013, ATAGI noted that there is inadequate statistical power to confirm or refute the possibility of 4CMenB causing febrile seizures, and the possibility of excess cases of vaccine-attributable febrile seizure if a toddler catch-up program is implemented cannot be dismissed. Prophylactic paracetamol use would reduce the rate of fever occurrence in infants in clinical practice. The likely uptake of routine prophylactic paracetamol in the Australian community was unknown. There was, however, a lack of evidence of effective prevention of febrile seizures with paracetamol use, and evidence of lack of effectiveness in prevention of recurrence of febrile seizures with paracetamol use among those with history of febrile seizures. In rare circumstances, febrile seizures may result in long-term impacts. The PBAC also noted that there may be a loss of confidence in immunisation arising from concerns about increased rates of fever and seizures.

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

### **Clinical claim**

- 6.12 The resubmission 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 and remained uncertain.
- 6.13 The PBAC agreed in November 2013 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 had also considered that the clinical claim was highly uncertain because of the likely short persistence of the antibody response, the unknown effect upon carriage of the bacteria, and the overall uncertain long-term protective efficacy against infection and disease.
- 6.14 The PBAC agreed in November 2013 that, in general, the local transient reactogenicity of 4CMenB was not different to routine vaccination, noting the rates of fever in infant participants of the trials receiving the vaccine and agreed that prophylactic paracetamol would be appropriate.

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

## Economic analysis

- 6.15 The resubmission presented a modelled economic evaluation (cost utility analysis) which was the same model as previously considered, except that only one scenario is presented and the discount rate applied in the base case is 5% per annum for costs and health outcomes. Some cost estimates and population inputs were also updated.
- 6.16 The ESC noted the reliance on the "ESC method", as summarised in Table C.2.2 of the commentary, was appropriate, but the method still favoured the vaccine. For example, the ESC agreed that vaccine effectiveness against NHBA could be questioned given the limited evidence available, and removing this effect would substantially increase the ICER. The ESC supported the previous ATAGI advice that it would be reasonable to exclude vaccine effectiveness against NHBA (i.e. lower bound of 54.2%) as a sensitivity analysis in the model.

### Summary of model structure and rationale

Component	Summary
Methods used to generate results	Stage 1: Dynamic transmission model; Stage 2: Combined Stage 1 with decision analytic model.
Epidemiology	<ul style="list-style-type: none"> <li>- Initial age-specific distribution of overall meningococcal carriage (all serotypes) based on a meta-analysis of carriage in multiple countries by Christensen (2010).</li> <li>- Incidence of IMD based on average cases of meningococcal B from 2000-2011 from NNDSS. Confirmed cases, plus imputation rule (Method 1) of probable, and not-determined.</li> <li>- The proportion of carriage that is vaccine-preventable was based on NNDSS data regarding IMD by serotype and MATS coverage by serotype.</li> </ul>
Transition probabilities (infection parameters)	Model calibration was used to estimate: <ul style="list-style-type: none"> <li>- the force of infection by age and whether vaccine-preventable (<math>\lambda</math>);</li> <li>- age-group-pair specific probabilities of effective contact (<math>\beta_{ij}</math>); and</li> <li>- risk of IMD given carriage by age and whether vaccine-preventable (<math>\theta</math>).</li> </ul>
Scenarios	Routine vaccination with 4CMenB among infant and adolescent with catch-ups in older infants, toddlers and adolescents.
Comparator	No vaccination.
Costs	Direct medical costs, including: administration; treatment of sequelae, and; treatment of relevant AEs. Non-direct medical costs, including: special education associated with sequelae and public health response (reporting, surveillance and chemoprophylaxis costs)*.
Perspective	Modified societal/health system – includes special education and public health response*.
Time horizon	100 years in the model base case versus up to 28-30 months after last dose in trials (V72P6E1).
Cycle length	0.01 months (approximately 7 hours), although transmission between different states occur on a monthly basis (every 100 time steps). A half-cycle correction was not applied. As the cycle length is 7 hours it is unlikely to affect the results.
Outcomes	Cases of vaccine preventable disease, long-term sequelae resulting from vaccine-preventable disease (limb amputation, hearing loss, seizures, renal insufficiency, significant neurological deficits, skin scarring), deaths, life years and QALYs.
Discount rate	The standard PBAC discounting approach: 5% per annum for costs and 5% per annum for health outcomes. Sensitivity analyses are conducted by applying: <ul style="list-style-type: none"> <li>a) a differential discounting approach (5% per annum for costs/█% per annum for health outcomes);</li> <li>b) a stepped discounting approach (5% per annum for costs/5% per annum for health outcomes for the first 20 years and █% per annum for costs/█% per annum for health outcomes thereafter); and</li> <li>c) a stepped/differential discounting approach (5% per annum for costs/5% per annum for health outcomes for the first █ and 5% per annum for costs/█% per annum for health outcomes thereafter).</li> </ul>

AE = adverse event; IMD = invasive meningococcal B disease; QALY = quality adjusted life years.

\* Productivity costs due to IMD included as sensitivity analysis. Source: Table D.3.1 of the commentary.

6.17 The key drivers of the model were as follows.

Description	Method/value	Impact
Discount rate	5% per annum for costs/5% per annum for health outcomes	High, differential and stepped/differential discounting favours 4CMenB
Time horizon	100 years; assumed from up to 28-30 month after last dose in trials (V72P6E1)	Moderate, favours 4CMenB
Vaccine efficacy	Assumed (various)	Moderate, favours 4CMenB
Mean persistence	Assumed (various)	Moderate, favours 4CMenB
Vaccine efficacy against carriage acquisition (herd immunity)	█%; based on V72_29	Moderate, if herd immunity >█% favours 4CMenB. If herd immunity <█% favours comparator

Source: Table 7 of the commentary.

6.18 The results of the stepped economic evaluation were as follows.

Step and component	4CMenB	No vaccination	Increment
<b>Step 1: cases averted over 100 years</b>			
Costs (\$)	█	█	█
Cases	█	█	█
<b>Incremental cost/extra case averted (\$)</b>			
<b>Step 2a: deaths averted over 100 years</b>			
Costs (\$)	█	█	█
Deaths	█	█	█
<b>Incremental cost/extra death averted (\$)</b>			
<b>Step 2b: life years lost over 100 years</b>			
Costs (\$)	█	█	█
Life years lost	█	█	█
<b>Incremental cost/extra life year gained</b>			
<b>Step 3: QALY lost over 100 years</b>			
Costs (\$)	█	█	█
QALYs lost	█	█	█
<b>Incremental cost/extra QALY gained (\$)</b>			
<b>QALY lost over 100 years in the previous submission considered in November 2013</b> (Scenario 6 versus no vaccination, discounted at 5% per annum for costs and █% per annum for health outcomes, 50% herd immunity, \$█ per dose + █% discount for catch-up)			
Costs	█	█	█
QALYs lost	█	█	█
<b>Incremental cost/extra QALY gained (\$)</b>			
<b>QALY lost over 100 years using the PBAC-preferred approach in November 2013</b> (Scenario 6 versus no vaccination, discounted at 5% per annum for costs and 5% per annum for health outcomes, █% herd immunity, \$█ per dose)			
<b>Incremental cost/extra QALY gained (\$)</b>			

Source: Table D.5.3 of the commentary.

6.19 In the previous submission, differential discount rates of 5% per annum for costs and █% per annum for health outcomes were proposed in the base case scenario. In the resubmission, a discount rate of 5% per annum was applied to both costs and health outcomes, consistent with the PBAC-preferred approach as stated in the PBAC Ratified Minutes 6-8 November 2013, item 6.37.

6.20 The ESC considered the use of a 5% per annum discount rate for both costs and health outcomes was consistent with the advice reaffirmed by the PBAC in the November 2013 consideration of this item, as well as for other proposed NIP listings. The ESC noted the brief review of discounting in Attachment F of the commentary, and advised that it supported retention of the current position, particularly for consistency across all evaluations.

- 6.21 Consequently, compared to the previous submission, the ICER increased substantially (more than \$200,000/QALY versus \$45,000 - \$75,000/QALY); however the ICER is largely unchanged compared to the ICER resulting from the PBAC-preferred approach (\$309,344/QALY as per PBAC Ratified Minutes 6-8 November 2013, item 6.37). The ESC proposed that a price reduction to align the ICER with the previous submission (\$45,000 - \$75,000/QALY) may be appropriate. The Pre-PBAC response stated that the sponsor would not support a price reduction to \$■■■■ as proposed by the ESC. The sponsor proposed a stepped non-differential discounting method: the discounting rate at ■■%/■■% and a price of \$■■/dose and ■■% price reduction on the catch-up program, then stepping to a lower discounting rate of ■■%/■■% with a concomitant price decrease to the equivalent of \$■■/dose after ■■. This alternate flat discount methodology results in the ICER of \$45,000 - \$75,000.
- 6.22 Univariate sensitivity analysis was presented in the resubmission on most parameters, and multivariate sensitivity analysis was presented in the resubmission on the estimate of Meningococcal Antigen Typing System (MATs) coverage and on discount rates. During the evaluation, univariate sensitivity analysis was conducted on applying the “ESC method” to estimate vaccine efficacy and persistence, and the use of a 2+1 schedule for infants and the time horizon. Multivariate sensitivity analysis was also conducted to reflect what may be a highly optimistic but feasible scenario.
- 6.23 The results of the sensitivity analyses indicated that the model was most sensitive to the discount rate followed by the use of the “ESC method” to estimate vaccine efficacy and persistence (particularly when natural immunity is taken into account). Even under a highly optimistic scenario (87% MATs coverage, 100% efficacy, ■■% herd immunity, and mean persistence in infants aged < 3 years is 120 months (i.e. 10 years)), the ICER remained high at \$105,000 - \$200,000/QALY when a discount rate of 5% per annum was applied to both costs and health outcomes. The ESC agreed that, even under highly optimistic assumptions, the ICER is still high. Consequently the ESC expressed doubt that the new information provided from the proposed studies in the proposed managed entry scheme would yield a cost-effective outcome at the current requested vaccine price.
- 6.24 The ESC noted that some costs in the context of general practice have not been considered, including additional consultation time. The ESC also noted the potential consequences of a fall in overall vaccine coverage that could occur as a result of lost confidence in vaccination arising from the increased rates of fever and febrile seizures should be considered.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**Estimated PBS usage & financial implications**

- 6.25 The estimated use and financial implications are shown in the table below.

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Number vaccinated	■■■■	■■■■	■■■■	■■■■	■■■■
Number vaccinated - Nov 2013	■■■■	■■■■	■■■■	■■■■	■■■■
Vaccinations	■■■■	■■■■	■■■■	■■■■	■■■■
Vaccinations - Nov 2013	■■■■	■■■■	■■■■	■■■■	■■■■

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated net cost to NIP/MBS *</b>					
Net cost to NIP					
Net cost to MBS					
Other costs to government					
<b>Estimated total net cost*</b>					
<b>Estimated net cost to NIP/MBS in the previous submission considered in November 2013 **</b>					
Net cost to NIP					
Net cost to MBS					
Other costs to government					
<b>Estimated total net cost in the previous submission considered in November 2013 **</b>					
<b>Estimated net cost to NIP/MBS considered at the November 2013 PBAC meeting ***</b>					
Net cost to NIP					
Net cost to MBS					
Other costs to government					
<b>Estimated total net cost considered at the November 2013 PBAC meeting ***</b>					

\* \$ per dose + % discount for catch-up program. \*\* \$ per dose + % discount for catch-up program. \*\*\* \$ per dose.  
Source: Table 9 of the commentary.

6.26 Due to uncertainty regarding uptake, the possibility that individuals receive less than the full vaccination schedule, the potential underestimation of the school implementation cost, the exclusion of MBS and hospitalisation costs associated with adverse events and avoided IMD cases, it was uncertain whether the net cost to government health budgets is over or underestimated. As noted for the cost-utility analysis, the financial analysis also excluded cost consequences to GPs, such as the increased need for a longer consultation time. The Pre-PBAC response acknowledged the high initial budget impact,

#### Proposed managed entry scheme

6.27 The resubmission proposed a managed entry scheme (MES) comprising four studies to address the clinical uncertainties.

- 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).
  - The ESC advised that this study would measure the change in incidence of IMD from the start of the proposed 4CMenB vaccination program and thereby provides an indication of its overall impact (direct and indirect effects). Because indirect (herd protection) effects are likely to take time to accrue, the relatively short time frame of five years is unlikely to be sufficient to capture these effects.
  - This is illustrated by the figure below, which demonstrates the varying reduction of all meningococcal B cases in Australia by different assumptions of herd protection if 4CMenB was implemented on the NIP in both infants and adolescents. It indicates that, even in the optimistic scenario where efficacy against carriage of MATS serotypes is 100%, only a 50% reduction in cases would be expected. The expected reduction in cases over the 100-year time horizon under the assumptions in the dynamic transmission model greatly depends upon vaccine impact on carriage. Given that true herd protection effects can only be determined once large population-based programs are in place, the ESC suggested that it may be informative to obtain comparable

follow-up data in jurisdictions implementing a population-based vaccination program (such as possibly Quebec and/or the UK) to provide some basis for estimating any herd protection effect.



- Program-related changes in incidence of IMD could be confounded by background natural fluctuation in incidence and by improvement in IMD case ascertainment (which would most likely bias against vaccination).
- The consequences of waning vaccine effectiveness over time for vaccinated individuals would not be measured.
- With a projected NNT of 10,532 over 5 years, the low incidence of IMD would render any estimates of vaccine effect imprecise.
- The ESC proposed that this study would provide a measure of (direct) vaccine effectiveness and possibly of persistence of protection, although there was insufficient detail provided about how these could be assessed to allow ATAGI to consider the necessity of additional booster doses.
- The proposed strategy of inferring vaccine effectiveness by measuring the change in meningococcal B isolates expressing MATS antigens (“MATS +ve”) as a proportion of overall meningococcal B isolates would be biased in favour of 4CMenB if the vaccination program induced replacement with MATS -ve isolates. In other words, if strain replacement occurred, the vaccine could appear highly effective even if no net impact occurred. Conversely, such an analysis would be biased against 4CMenB if the vaccine also reduced “MATS -ve” strains through an effect on sub-threshold MATS-antigen expressing strains.
- A vaccine effectiveness analytic study of 4CMenB in preventing IMD, including establishing a vaccine registry (observational study protocol V72\_53OB).
  - The ESC advised that such a case-control study would require collection and linkage of data that is not routinely linked and which in some cases is not currently collected (e.g. immunisation records for children > 7 years of age). The ESC advised that the logistical barriers were considerable.
  - The proposal to match cases with 3 controls among those registered in Australian Childhood Immunisation Register may result in significant underpowering of the study if vaccine coverage is high and the number of children receiving no doses is low. The ESC advised that the resubmission failed to consider the need to exclude partially vaccinated children from the proposed analysis which is likely to result in a significant overestimation of the power of the analysis.
  - Failure to control for potentially important confounders (e.g. socioeconomic status) and differences in ascertainment of vaccination status for cases and controls could significantly bias vaccine effectiveness estimation in either direction.
  - Even with optimistic assumptions, such a study was considered unlikely to provide evidence of any protective effect within the timeframe of the analysis, let alone the required precision on age-specific and dose-dependent vaccine effectiveness required to reliably inform the economic model.

- A nasopharyngeal carriage survey of carriage of *Neisseria meningitidis* before and after the introduction of 4CMenB into the NIP (observational study protocol V72\_73OB).
- The ESC noted that direct vaccine protection against carriage is likely to be a pre-requisite for demonstrating an effect on herd protection, but is not in itself sufficient. Herd protection is also dependent on the nature and extent of mixing patterns between vaccinated and susceptible individuals. As such, evidence of effectiveness in reducing nasopharyngeal carriage should not be conflated with evidence of effectiveness in increasing herd protection.
- Evidence of an effect on herd protection would be strengthened by evidence of reduced nasopharyngeal carriage among unvaccinated as well as vaccinated individuals, particularly among infants who are at greatest risk of IMD.
- Because of the low baseline nasopharyngeal carriage expected in the target population, the ESC considered that impact on carriage might require an unfeasibly large sample size or would alternatively take several years to accumulate and might not be feasible within the timeframe of the proposed MES.
- Nasopharyngeal carriage in infants would not also be measured, which would mean that extrapolations of the study results in adolescents to other key populations could not be verified.
- A safety surveillance study, consisting of regular passive, enhanced and active pharmacovigilance.
- Considering the expressed concern of ATAGI on the potential for high reactogenicity to impact on parent confidence in the vaccine program overall, the ESC suggested that the proposed safety surveillance system should also specifically monitor for increased rates of vaccine delay/hesitancy and refusal across the NIP.

6.28 The re-submission did not explicitly state which variables from which studies would be used in the revised model to subsequently inform pricing (and recoding of the model may be required), nor did it specify the target ICER. The ESC noted that generating revised variables would also not reduce the significant uncertainty inherent in the structural assumptions required to construct the dynamic transmission model, such as minimising natural fluctuations in incidence of IMD. It would be crucial to link vaccination status to timing and severity of disease as the vaccine effect could be underestimated due herd immunity.

6.29 The ESC agreed with the PBAC's previous concerns about the feasibility of removing 4CMenB from the NIP in the event of the results of the MES being less than the projected effects (i.e. beyond a disinvestment which could be satisfactorily addressed by a reduction in price). The ESC was also concerned that there remained a risk that the results of the MES may not be sufficiently conclusive as a basis to draw any revised conclusions about the incremental cost-effectiveness of 4CmenB.

6.30 The ESC noted the proposed governance arrangements for the MES and the role of the sponsor in these arrangements. Considering the vested interests of the sponsor in the results of the MES studies, the ESC suggested that it would be appropriate for the sponsor to have only a non-determinative ex officio role on the Scientific Steering Committee.

6.31 The post-submission advice from ATAGI stated: Notwithstanding the identified clinical uncertainties, implementation issues and challenges outlined within this and previous ATAGI advice, ATAGI supports inclusion of the multicomponent meningococcal B vaccine (4CMenB) on the National Immunisation Program (NIP)

through a Managed Entry Scheme (MES) in a 3+1 infant schedule and adolescent program.

- 6.32 As the NIP is a joint initiative between the Commonwealth and states and territories, the Commonwealth Chief Medical Officer (CMO) sought the views of the Chief Health Officers (CHO) in each of the states and territories about the feasibility of an MES and willingness to implement it in each jurisdiction. The Department's Office of Health Protection provided a consolidated response from the CHOs of the states and territories.
- 6.33 While the scale of the MES studies should take feasibility considerations into account, the ESC also noted that the sponsor's proposed expenditure on the MES (less than \$██████ over 5 years) would represent only one thousandth of the proposed net government expenditure on the 4CMenB program over the same period. As the requested price was larger than would be justified by the base case of the cost-effectiveness analysis, and no prospective or retrospective rebate was proposed for the period of the MES, the balance of financial risks was therefore very much in favour of the sponsor. In response to the assessment of the MES, the sponsor committed in good faith to a reasonable increase of their original financial commitment to the MES in the Pre-PBAC response.

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

## **7 PBAC Outcome**

- 7.1 The PBAC rejected the resubmission requesting listing of the 4CMenB vaccine on the National Immunisation Program Schedule for the prevention of meningococcal B disease in infants and adolescents.
- 7.2 The resubmission was rejected on the basis of 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.
- 7.3 The PBAC noted the clinical need for vaccination against meningococcal B disease considering the rapid onset of disease following infection, and given that clinical improvements in the diagnosis and management of the infection have had little impact on IMD outcomes. The PBAC noted the strong consumer support for this submission, highlighting the community's desire to overcome IMD and its consequences.
- 7.4 The PBAC agreed that the nominated comparator was appropriate, given that no vaccine against meningococcal B infection is currently available.
- 7.5 The PBAC noted that no direct evidence was presented regarding vaccine efficacy against infection and disease. The PBAC acknowledged the limitations in conducting randomised controlled trials measuring clinical outcomes for this vaccine due to the nature of the disease and the low number of total cases in Australia; however this lack of directly relevant data leads to multiple uncertainties in relation to the magnitude of clinical effectiveness against the disease.
- 7.6 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.

- 7.7 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 ESC, the PBAC also noted that safety in adolescents appears acceptable.
- 7.8 The PBAC concluded that the re-submission's base case ICER of more than \$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. 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. The PBAC 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. 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 (ie \$45,000/QALY - \$75,000/QALY) was likely to be the only available option for further PBAC consideration.
- 7.9 The ICER remains highly sensitive to the discount rates applied to costs and outcomes. The PBAC noted the sponsor's proposal of a stepped non-differential discounting method with a price reduction after [REDACTED]. The PBAC considered that the resulting ICER of \$45,000/QALY - \$75,000/QALY was not acceptable. The PBAC reaffirmed its preference for applying a discount rate of 5% per annum for both costs and outcomes. The PBAC considered that this was supported by the brief review of the literature on discounting in the commentary and by the ESC advice, which emphasised the importance of adopting a consistent approach on discounting across all evaluations.
- 7.10 The PBAC noted the proposal in the Pre-PBAC response to offer [REDACTED], however the costs and implications of this proposal have not been evaluated ..
- 7.11 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. 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.

7.12 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.

7.13 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**

Novartis Vaccines disagrees with the decision. Novartis notes that the licensure of this vaccine by the TGA and the clinical recommendations on use from ATAGI are based on a positive assessment of the vaccines clinical effectiveness and safety.

The current methodology of cost-effectiveness developed for therapeutic interventions significantly underestimates the long term value of vaccinations, and the rare but devastating impact of meningococcal meningitis on children and their families.

In relation to Studies V72P12 and V72P13, we disagree with the PBAC's comments on febrile seizures which is based on studies not powered to show a difference and hence it is not appropriate to draw conclusions on the number of febrile seizures expected based on number of vaccinations; statistically there was no difference between the active and control group which is acknowledged by ATAGI. Furthermore, we point out ATAGI's clinical recommendation on the use of prophylactic paracetamol with every dose of 4CMenB administered to children <2 years of age to reduce probability and severity of fever which will reflect the real life experience of this vaccine as opposed to the clinical trial experience where prophylactic paracetamol was not used. Recent experience in the Quebec public program has shown 93% uptake of prophylactic paracetamol in infants and toddlers with corresponding reduction in fever.

