5.09 MENINGOCOCCAL (GROUPS A, C, W-135 and Y) OLIGOSACCHARIDE CRM 197 CONJUGATE VACCINE Pre-filled syringe, 0.5mL, Menveo®, GlaxoSmithKline Australia Pty Ltd

1 Purpose of Application

1.1 NIP listing for a meningococcal serogroup A, C, W-135 and Y oligosaccharides conjugated individually to Corynebacterium diphtheriae CRM197 protein (MenACWY-CRM) vaccine for the prevention of invasive meningococcal disease (IMD) caused by Neisseria meningitidis serogroups A, C, W_{135}, and Y (MenA, MenC, $MenW_{135}$ and MenY, respectively) in adolescents. The PBAC had not previously considered this vaccine.

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

Component	Description
Population	Adolescents aged approximately 15 years of age (Year 9 or 10 students), with a catch-up program for adolescents/ young adults aged up to and including 19 years.
Intervention	A single dose of the MenACWY-CRM vaccine (Menveo®). An extra dose of vaccine in adolescents with medical conditions that increase the risk of IMD is recommended.
Comparator	No main comparator specified. The MenACWY-TT (Nimenrix®) and MenACWY-DT (Menactra®) vaccines as near market comparators. The PSCR noted the main comparator in the submission was 'no vaccine' or placebo.
Outcomes	Seroresponse, hSBA titres, GMTs, reactivity and adverse events
Clinical claim	• MenACWY-CRM is immunogenic in the adolescent age group (average age 15 years) against the four N. meningitidis serogroups A, C, W and Y • MenACWY-CRM may be co-administered with routine vaccinations given to adolescents within the NIP • Adolescent subjects vaccinated with a single dose of MenACWY-CRM demonstrated a sustained immune response up to 5 years post vaccination • There is no evidence of a difference in the immunogenicity or safety of MenACWY-CRM and MenACWY-TT • MenACWY-CRM is well tolerated, with an acceptable safety profile

hSBA: human serum bactericidal assay; IMD: invasive meningococcal disease; GMT: Geometric mean titers; MenACWY-CRM: Meningococcal Oligosaccharide CRM197 Conjugate Vaccine; MenACWY-TT: Meningococcal polysaccharide tetanus toxoid conjugate vaccine; MenACWY-DT: Meningococcal polysaccharide diphtheria toxoid conjugate vaccine; PSCR: Pre Sub-Committee response
Source: Compiled during the evaluation

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

2 Requested listing

2.1 Suggestions and additions proposed to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Table 2: Essential elements of the requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Proposed approved ex-manufacturing price	Proprietary name and manufacturer
Meningococcal (Groups A, C, W-135 and Y) Oligosaccharide CRM197 Conjugate Vaccine powder and solvent for solution for injection Pre-filled syringe, 0.5mL	1	1	0	$[redacted]	Menveo, GlaxoSmithKline Australia Pty Ltd

Category/Program – NIP

Routine NIP indication:

- A single dose of Menveo (MenACWY-CRM) for adolescents aged *14 to 16* ~~approximately 15~~ years old (administered via a school-based program * OR
- A single dose of Menveo (MenACWY-CRM) for adolescents aged up to 19 years administered via a school-based catch-up program or accessed via the GP *(school-leavers)*.**

At high risk of developing IMD NIP indication:

- Two doses of Menveo (MenACWY-CRM) for adolescents aged *14 to 16* ~~approximately 15~~ years old (Year ~~9 or~~ 10 students) administered via a school-based program * OR
- Two doses of Menveo (MenACWY-CRM) for adolescents aged up to 19 years administered via a school-based catch-up program or accessed via the GP *(school-leavers)*.**

* For all adolescents in ~~year 9 or~~ year 10.

** For all adolescents *in year 11 and 12 (or school-leavers)* ~~(16-19 years old)~~ who did not receive the vaccination ~~through the routine vaccination~~ *in year 10.*

Source: compiled during the evaluation based on section 1.4, p32 of the submission.

2.2 The submission requested two NIP doses – one for routine vaccination of the proposed population, and an additional dose for adolescents with medical conditions that increase the risk of developing IMD, as defined in the Australian Immunisation Handbook (Part 4.10.7, List 4.10.1). This differed from the PBAC's recommended NIP listing for the meningococcal polysaccharide serogroups A, C, W135 and Y tetanus toxoid conjugate vaccine (MenACWY-TT, Nimenrix®) which did not include a request for an additional dose for the at-risk population. The ESC noted that although there was no proposed duration between the two doses for the at-risk population, the Australian Immunisation Handbook (Table 4.10.2) recommends that the second dose of MenACWY vaccine be given at an interval of 8 weeks for those aged over 7 years.[1] The Australian Immunisation Handbook also recommends that the at-risk patient population receive a booster dose every 5 years after the previous dose of MenACWY. The submission did not include a request for these booster doses.

2.3 The submission proposed an ex-manufacturer price of $[redacted] per dose of MenACWY-CRM, based on the nationally negotiated price for the MenC component of Hib-MenC conjugate vaccine which is NIP listed for use in infants.

[1] Department of Health. (2017a, August 1). 4.10 Meningococcal disease. Retrieved from THE AUSTRALIAN IMMUNISATION HANDBOOK 10TH EDITION: http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10part4~handbook10-4-10

2.4 The submission estimated the cost of the catch-up program for Year 1 (2019) only, suggesting that the catch-up program is a short-term, non-ongoing program. Specifically, the submission stated that "The Australian population aged 16-19 years is only included for the first forecast year, as this represents patients in a catch-up program and is not an ongoing eligible population. Although there may be a degree of uncertainty as to whether all adolescents eligible for a catch-up vaccination will be vaccinated in the first year of listing, this calculation nevertheless represents the total eligible population for a catch-up dose".

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

3 Background

Registration status

3.1 The MenACWY-CRM vaccine was registered on the ARTG on 20 May 2010 for: active immunisation of infants and children (from 2 months of age), adolescents and adults to prevent invasive disease caused by Neisseria meningitidis serogroups A, C, W-135 and Y.

Previous PBAC consideration

3.2 The PBAC had not previously considered the MenACWY-CRM vaccine.

3.3 The PBAC recommended listing MenACWY-TT (Nimenrix®) on the NIP for adolescents in March 2018.[2] The PBAC also recommended MenACWY-TT for listing on the NIP for infants in January 2018[3].

4 Population and disease

4.1 IMD is a rare disease caused by the bacterium Neisseria meningitidis. IMD can also cause meningitis and septicaemia. Meningococcal disease can progress rapidly to serious disease and have a high mortality rate (5-10%), despite appropriate antibiotic therapy. About 10-30% of meningococcal disease survivors have permanent sequelae, including limb deformity, skin scarring, deafness and neurologic deficits[4].

[2] PBAC (March 2018) Public summary document: Meningococcal polysaccharide conjugate vaccine serogroups A, C, W-135 and Y (adolescents), pre-filled syringe, 0.5mL, Nimenrix

[3] PBAC (March 2018) Public summary document: Meningococcal polysaccharide conjugate vaccine serogroups A, C, W-135 and Y (infants), pre-filled syringe, 0.5mL, Nimenrix

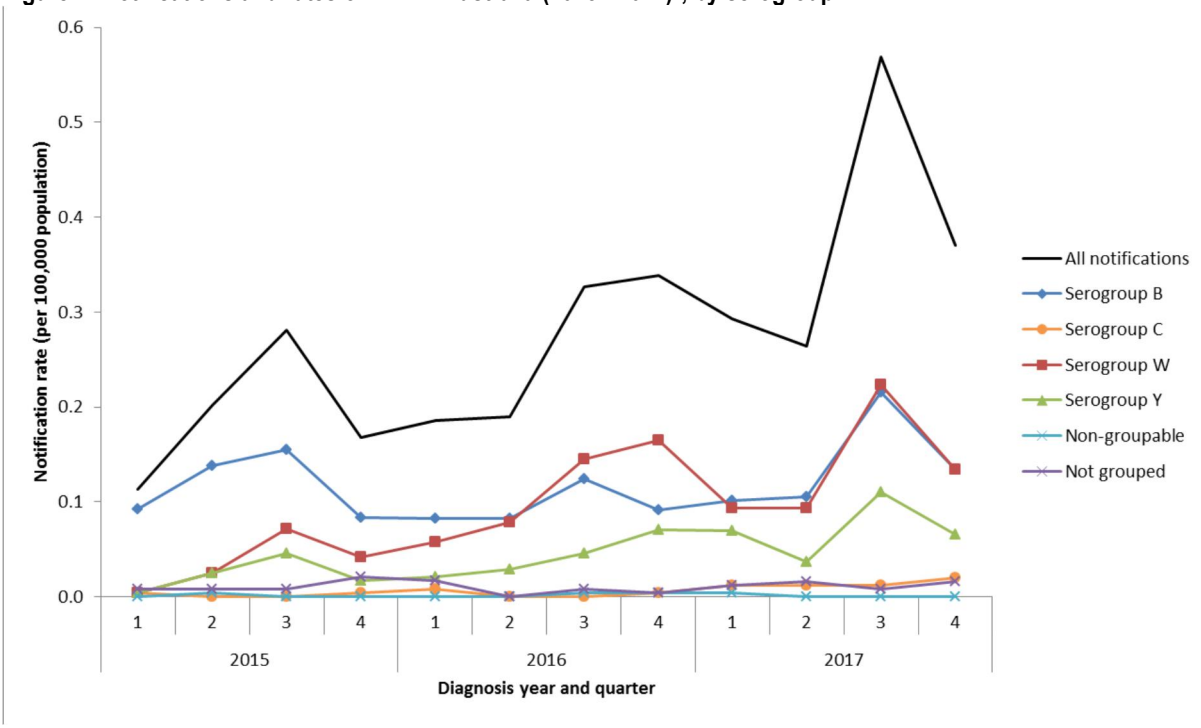
[4] Department of Health. (2017a, August 1). 4.10 Meningococcal disease. Retrieved from THE AUSTRALIAN IMMUNISATION HANDBOOK 10TH EDITION: http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10part4~handbook10-4-10

Department of Health. (2017b, December 11). *Meningococcal disease*. Retrieved from Conditions and diseases: https://beta.health.gov.au/conditions-and-diseases/meningococcal-disease

Across age groups, incidence peaks for infants and adolescents. The case fatality rate for all cases of IMD is around 4.7%, however may be higher for $MenW_{135}$.[5]

4.2 There has been an increase in the number of cases caused by MenW and MenY in recent years (see Figure 1). The ESC noted the increase in total incidence of meningococcal disease is driven by the increase in Y and W strains (as well as serogroup B), and noted the high case fatality rate associated with W strain (ATAGI Pre-submission advice, P6). The ESC noted that a decrease in incidence of C strain was seen after introduction of the meningococcal C vaccine. However, a range of factors remain unknown with regard to predicting efficacy for MenACWY-CRM, including the unpredictability of the natural history of meningococcal disease.

Figure 1: Notifications and rates of IMD in Australia (2015 - 2017)*, by serogroup



*Data shown is for cases with a diagnosis date from 1 January 2015 onwards, as of 14 December 2017. Rates for Q4 2017 have not been adjusted for the incomplete observation period of Q4.
Source: Figure 2, p5 of ATAGI pre-submission advice.

4.3 There were 379 notified cases of IMD in Australia in 2017, of which 87 cases of IMD were caused by MenACWY and were in infants (0-4 years old), and 41 cases of IMD were caused by MenACWY and were in adolescents (15-19 years old) (National Notifiable Diseases Surveillance System, NNDSS).[6] The ESC noted ATAGI's advice that a key population group that would most benefit from a MenACWY vaccine was

[5] Australian Government Department of Health (2016) Summary of National Surveillance Data on Vaccine Preventable Diseases in Australia, 2008–2011, Communicable Diseases Intelligence, Volume 40
[6] Australian Government Department of Health (2017) Notifications of a selected disease by age group, sex and year, Available: http://www9.health.gov.au/cda/source/rpt_5_sel.cfm. Accessed 18 April 2018.

adolescents aged approximately 14 to 19 years old.

4.4 Currently there are several State-based meningococcal programs for the provision of meningococcal serogroups A, C, W_{135} and Y (MenACWY) vaccines, including MenACWY-CRM, MenACWY-TT and meningococcal polysaccharide diphtheria toxoid conjugate (MenACWY-DT) vaccine (Menactra®), to varied patient groups. The Pre-Sub-Committee Response (PSCR) noted the 2017 IMD notification rates due to meningococcal W exceeded the 2016 rates in all age groups except the 15-19 and 25-44 year groups, and suggested this may be due to the State-based adolescent MenACWY vaccination programs. The ESC considered that the variation in rates may be due to the State-based vaccination programs, but the data supporting this is currently very limited.

4.5 The PSCR and Pre-PBAC Response acknowledged the State-based programs may cease with a NIP listing, and claimed that the availability of two MenACWY vaccines through the NIP would improve surety of supply. The ESC noted the value of having more than one vaccine available for NIP listing on the designated vaccines list. The ESC noted that MenACWY vaccination is also well established for use in the private market.

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

5 Comparator

5.1 The submission did not nominate a main comparator. The submission nominated MenACWY-TT as a near-market comparator given that a PBAC submission for the MenACWY-TT vaccine for immunisation of adolescents in Year 10 and a catch-up program via school or GP was considered for listing on the NIP in March 2018. The ESC considered 'no vaccine' (placebo) to be an appropriate comparator and MenACWY-TT to be an appropriate near market comparator, noting MenACWY-TT was recommended for inclusion on the NIP at the March 2018 PBAC meeting.

5.2 The submission also considered the MenACWY-DT vaccine (Menactra®) as a second near-market comparator given it is supplied in the State-based programs. The MenACWY-DT vaccine is not listed on the NIP. The PBAC had not previously considered a submission for NIP listing of this vaccine and it was not on the agenda for the July 2018 PBAC meeting.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from an individual (1) and an organisation (1), Meningitis Centre Australia, via the Consumer Comments facility on the PBS website. The comments noted the increase in prevalence of the W and Y strains of meningococcal disease, the varying expense and availability of MenACWY vaccination on the private market and the benefit of preventing death and disability resulting from meningococcal disease.

Clinical trials

6.3 The submission was based on four key RCTs, comparing the MenACWY-CRM (Menveo) vaccine to either placebo or a comparator meningococcal vaccine. The four key RCTs compared:

- Ishola 2015: MenACWY-CRM (Menveo) to MenACWY-TT (Nimenrix) (N=93)
- V59P13: MenACWY-CRM (Menveo) to MenACWY-DT (Menactra) (N=2180)
- V59P6: MenACWY-CRM (Menveo) to MenACWY (Menomune) (N=524)
- V59_39d: MenACWY-CRM (Menveo) to placebo (N=450)

6.4 Three of the clinical trials presented also had subsequent persistence extensions.

6.5 Five supplementary RCTs and four open-label studies were also presented to support claims of efficacy with concomitant vaccines or claims regarding safety.

6.6 The submission also presented a naïve indirect comparison of the MenACWY-CRM vaccine (Menveo) to the MenACWY-TT vaccine (Nimenrix) using the MenACWY-DT vaccine (Menactra) as the common comparator, based on the following trials:

- V59P13: Compared the MenACWY-CRM vaccine to the MenACWY-DT vaccine (N=2,180 and 1,359)
- MenACWY-TT-071: Compared the MenACWY-TT vaccine to the MenACWY-DT vaccine (N=1,016)
- MenACWY-TT-052: Compared the MenACWY-TT vaccine to the MenACWY-DT vaccine (N=872)

6.7 Details of the trials presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Menveo Comparative trials		
V59_39d	A phase 3, multi-center, observer-blind, placebo controlled, randomized study to evaluate the immunogenicity and safety of Novartis Meningococcal ACWY conjugate vaccine in healthy subjects from 11 to 55 years of age in Korea	October 2011
	Lee HJ, Chung MH, Kim WJ, et al. Immunogenicity and safety of a novel quadrivalent meningococcal conjugate vaccine (MenACWY-CRM) in healthy Korean adolescents and adults.	Int J Infect Dis 2014;28:204-10
V59P13	A Phase 3, Randomized, Observer-blind, Controlled, Multi-Center Study to Evaluate the Lot to Lot Consistency of Novartis Meningococcal ACWY Conjugate Vaccine when One Dose is Administered to Healthy Adolescents 11-18 Years of Age and to Compare the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine with that of Licensed Meningococcal ACWY Conjugate Vaccine (Menactra™) when One Dose is Administered to Healthy Subjects 11-55 Years of Age.	April 2008
	Addendum to A Phase 3, Randomized, Observer-blind, Controlled, Multi-Center Study to Evaluate the Lot to Lot Consistency of Novartis Meningococcal ACWY Conjugate Vaccine when One Dose is Administered to Healthy Adolescents 11-18 Years of Age and to Compare the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine with that of Licensed Meningococcal ACWY Conjugate Vaccine (Menactra™) when One Dose is Administered to Healthy Subjects 11-55 Years of Age.	December 2008
	Addendum to A Phase 3, Randomized, Observer-blind, Controlled, Multi-Center Study to Evaluate the Lot to Lot Consistency of Novartis Meningococcal ACWY Conjugate Vaccine when One Dose is Administered to Healthy Adolescents 11-18 Years of Age and to Compare the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine with that of Licensed Meningococcal ACWY Conjugate Vaccine (Menactra™) when One Dose is Administered to Healthy Subjects 11-55 Years of Age.	August 2011
	Jackson L.A, Baxter R, Reisinger K. Phase III comparison of an investigational quadrivalent meningococcal conjugate vaccine with the licensed meningococcal ACWY conjugate vaccine in adolescents.	Clinical Infectious Diseases. 49 (1) (pp e1-e10), 2009.
V59P13E1	An Open-Label, Multi-Center Study to Evaluate the Persistence Of Antibody Responses Among Adolescents Who Previously Received MenACWY-CRM Conjugate Vaccine or Menactra®	July 2013
	Baxter R, Reisinger K, Block SL, et al. Antibody persistence after primary and booster doses of a quadrivalent meningococcal conjugate vaccine in adolescents.	Pediatr Infect Dis J. 2014;33(11):1169-1176.
	Baxter R, Reisinger K, Block SL. Antibody persistence and booster response of a quadrivalent meningococcal conjugate vaccine in adolescents.	Journal of Pediatrics. 2014;164(6):1409-15
	Gill C.J, Baxter R, Anemona A et al. Persistence of immune responses after a single dose of Novartis meningococcal serogroup A, C, W-135 and Y CRM-197 conjugate vaccine (Menveo) or Menactra among healthy adolescents.	Human Vaccines. 2010;6(11): 881-887
V59P6	A Phase 2, Randomized, Single-blind, Controlled, Multicenter Study to Compare the Safety and Immune Response of One Dose of Chiron Meningococcal ACWY Conjugate Vaccine With or Without Aluminum Phosphate Adjuvant With the Safety and Immune Response of One Dose of Licensed Meningococcal ACWY Polysaccharide Vaccine (Menomune®) Administered to Healthy Adolescents 11 to 17 Years of Age.	March 2008

Trial ID	Protocol title/ Publication title	Publication citation
	Jackson LA, Jacobson RM, Reisinger KS et al. A randomized trial to determine the tolerability and immunogenicity of a quadrivalent meningococcal glycoconjugate vaccine in healthy adolescents.	Pediatric Infectious Disease Journal. 28 (2) (pp 86-91), 2009.
V59P6E1	Phase 2b, Open-Label, Multi-Center Study to Evaluate the Persistence of Antibody Response and to Assess the Immune Response to a Booster Dose of MenACWY Conjugate Vaccine in Subjects Previously Vaccinated as Adolescents with Either MenACWY Conjugate Vaccine or Menomune®	June 2011
	Jacobson RM, Jackson LA, Reisinger K, Izu A, Odrljin T, Dull PM. Antibody persistence and response to a booster dose of a quadrivalent conjugate vaccine for meningococcal disease in adolescents.	Pediatr Infect Dis J. 2013;32(4):e170-e177.
Ishola 2015	Ishola D, Andrews N, Waight P. Randomized Trial to Compare the Immunogenicity and Safety of a CRM or TT Conjugated Quadrivalent Meningococcal Vaccine in Teenagers who Received a CRM or TT Conjugated Serogroup C Vaccine at Preschool Age.	Pediatr Infect Dis J 2015;34:865–874
Menveo comparative trials in which a single arm was analysed		
V102-02	Phase 2, Observer Blinded, Controlled, Randomized Multi-Center Study in Adolescents, to Evaluate Safety, Tolerability and Immunogenicity of Four Different rMenB plus MenACWY Formulations. Saez-Llorens X, Vaca D.C.A, Abarca K. Immunogenicity and safety of investigational vaccine formulations against meningococcal serogroups A, B, C, W, and Y in healthy adolescents.	March 2013 Human Vaccines and Immunotherapeutics. 11 (6) (pp 1507-1517), 2015.
V102-03	Phase 2, Observer Blinded, Controlled, Randomized Multi-Center Study in Adolescents and Young Adults to Evaluate Safety and Immunogenicity of Two Different rMenB with OMV + MenACWY Combination Vaccination Formulations. Block S.L, Szenborn L, Daly W. A comparative evaluation of two investigational meningococcal ABCWY vaccine formulations: Results of a phase 2 randomized, controlled trial.	December 2013 Vaccine 33 (2015) 2500–2510
V59P20E1	A Phase IV, Open-Label, Controlled, Multi-Center Study To Evaluate The 5-Year Antibody Persistence Among Children Who Previously Received Novartis MenACWY Conjugate Vaccine At 2 To 10 Years Of Age And To Assess The Immune Response To A Single Dose Of Novartis MenACWY Conjugate Vaccine Block SL, Christensen S, Verma B, et al. Antibody persistence 5 years after vaccination at 2 to 10 years of age with Quadrivalent MenACWY-CRM conjugate vaccine, and responses to a booster vaccination.	June 2014 Vaccine 2015;33:2175-82.
Menveo Single Arm Trials		
V59_43d	A phase 3, multi-center, open-label study to evaluate immunogenicity and safety of Novartis Meningococcal ACWY conjugate vaccine (MenACWY-CRM) in healthy subjects from 2 to 75 years of age in India.	November 2014
	Lalwani S, Agarkhedkar S, Gogtay N, et al. Safety and immunogenicity of an investigational meningococcal ACWY conjugate vaccine (MenACWY-CRM) in healthy Indian subjects aged 2 to 75 years.	Int J Infect Dis 2015;38:36-42.
V59_49d	A phase 3, multicenter, open-label study to evaluate immunogenicity and safety of Novartis Meningococcal ACWY conjugate vaccine (MenACWY-CRM) in healthy subjects from 2 to 18 years in Taiwan. Huang LM, Chiu NC, Yeh SJ, Bhusal C, Arora AK. Immunogenicity and safety of a single dose of a CRM-conjugated meningococcal ACWY vaccine in children and adolescents aged 2-18 years in Taiwan: results of an open label study.	January 2013 Vaccine 2014;32:5177-84.
V59_50d	A Phase 3, Multicenter, Open-label Study to Evaluate Immunogenicity and Safety of Novartis Meningococcal ACWY Conjugate Vaccine (MenACWY-CRM) in Healthy Children, Adolescents, and Adults in Russia	September 2013

Trial ID	Protocol title/ Publication title	Publication citation
	Ilyina N, Kharit S, Namazova-Baranova L, et al. Safety and immunogenicity of meningococcal ACWY CRM197-conjugate vaccine in children, adolescents and adults in Russia.	Hum Vaccin Immunother. 2014;10:2471-81.
Menveo with concominant vaccines		
V59P18	A Phase 3, Single Center, Open-label, Controlled, Randomized Study to Evaluate the Safety and Immunogenicity of Novartis MenACWY vaccine administered either alone or concomitantly with a Combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap, Boostrix®) and Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine (Gardasil®) in Healthy Adolescents.	February 2009
	Arguedas A, Soley C, Loaiza C, et al. Safety and immunogenicity of one dose of MenACWY-CRM, an investigational quadrivalent meningococcal glycoconjugate vaccine, when administered to adolescents concomitantly or sequentially with Tdap and HPV vaccines.	Vaccine. 2010;28(18):3171-3179.
V59P11	A Phase 3, Multi-Center, Observer Blind, Controlled, Randomized Study to Compare the Immunogenicity and Safety of the Concomitant Administration of a Combined Tetanus, Reduced Diphtheria and Acellular Pertussis (Tdap) Vaccine (GSK Boostrix®) and Novartis (formerly Chiron) Meningococcal ACWY Conjugate Vaccine, With Either One Dose of Boostrix®, or One Dose of Novartis Meningococcal ACWY Conjugate Vaccine in Healthy Subjects Aged 11-25 Years	December 2007
	Gasparini R, Conversano M, Bona G, et al. Randomised trial on the safety, tolerability, and immunogenicity of MenACWY-CRM, an investigational quadrivalent meningococcal glycoconjugate vaccine, administered concomitantly with a combined tetanus, reduced diphtheria, and acellular pertussis vaccine in adolescents and young adults.	Clin Vaccine Immunol. 2010;17(4):537-544.
V59_40	A Phase 4, Placebo-Controlled, Randomized Study to Evaluate the Immunogenicity and Safety of a Combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap, Boostrix®) and Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine (Gardasil®) in Healthy Adolescents when Administered with MenACWY Conjugate Vaccine	October 2013
	Gasparini R, Johnston W, Conversano M, et al. Immunogenicity and safety of combined tetanus, reduced diphtheria, acellular pertussis vaccine when co-administered with quadrivalent meningococcal conjugate and human papillomavirus vaccines in healthy adolescents.	J Vaccines Vaccin. 2014;5:231. doi: 10.4172/2157-7560.1000231.
Menveo safety		
Holmes AD 2018	Holmes A.D, Abbasi O.Z. Jacoby J.L. Systemic lupus erythematosus following meningococcal vaccination.	American Journal of Emergency Medicine. 36 (1) (pp 170.e3-170.e4), 2018.

Source: Table 2.3, p42-44 of the submission

6.8 Key features of the direct randomised trials are summarised in Table 4.

6.9 The study by Ishola 2015 was the only study that compared MenACWY-CRM to MenACWY-TT. It is unclear whether the study by Ishola 2015 was blinded. It did not report the proportion achieving seroresponse. The study was small and not powered to test for non-inferiority between the vaccines.

Table 4: Key features of the included evidence

Study name	Study design	Intervention (arm of interest)	Comparator	N (enrolled)	Patient population	Outcomes
Key comparative trials						
Ishola 2015	R, Unknown	MenACWY-CRM	MenACWY-TT	93	16-19 years with previous MenC vaccination (3-6 years)	% rSBA ≥ 1:8 and ≥ 4-fold rises in SBA titre* GMTs *Assumed to be rSBA
V59P13	R, OB	MenACWY-CRM	MenACWY-DT	3539	11-18 years; and 11-55 years	% (hSBA) seroresponse % hSBA ≥ 1:4 and 1:8 GMTs
V59P6	R, SB	MenACWY-CRM	MenACWY (Menomune)	524	11-17 years	% hSBA ≥ 1:4 and 1:8 GMTs
V59_39d	R, Unknown	MenACWY-CRM	Placebo	450	11-55 years (Korean)	% (hSBA) seroresponse % hSBA ≥ 1:8 GMTs
Supplementary Trials						
MenACWY-CRM with concomitant vaccines to show no reduction in efficacy for giving vaccines together						
V59P18	R, OL	MenACWY-CRM + Tdap + HPV	MenACWY-CRM → Tdap → HPV; Tdap→ MenACWY-CRM →HPV	1620	11-18 years	% (hSBA) seroresponse % hSBA ≥ 1:8
V59P11	R, OB	MenACWY-CRM + Tdap	MenACWY-CRM + Placebo; Tdap	1072	11-25 years	% hSBA ≥ 1:8
V59_40e	R, Unknown	MenACWY-CRM + Tdap + HPV	Placebo + Tdap + HPV	801	11-18 years	% (hSBA) seroresponse % hSBA ≥ 1:8
Other MenACWY-CRM trials						
V102-02	R, OB	MenACWY-CRM	Investigational products	495	Not reported	% of subjects with hSBA ≥1:8, and hSBA geometric mean titers (GMTs)
V103-03	R, OB	MenACWY-CRM	Investigational products	484	10-25 years	immunogenicity hSBA assessed at day 30 post vaccination Study design allowed a placebo comparison (cross over)
V59P20E1	OL	MenACWY-CRM	Investigational products	465	11-15 years	immunogenicity assessed at day 28 hSBA

Study name	Study design	Intervention (arm of interest)	Comparator	N (enrolled)	Patient population	Outcomes
V59_43d	OL	MenACWY-CRM	None	180	11 - 18 years	% (hSBA) seroresponse* hSBA ≥1:8
V59_49d	OL	MenACWY-CRM	None	341	11-18 years	hSBA seroresponse hSBA ≥ 1:8
V59_50d	OL	MenACWY-CRM	None	198	11-17 years	hSBA seroresponse hSBA titer ≥ 1:8
Informal indirect comparison						
MenACWY-TT-071	R, OB	MenACWY-TT	MenACWY-DT	1016	10-25 years	% (hSBA) seroresponse % hSBA ≥ 1:8 GMTs
MenACWY-TT-052	R, SB	MenACWY-TT	MenACWY-DT	872	10-25 years	Vaccine response % hSBA ≥ 1:8 GMTs

R: randomised; hSBA: human serum bactericidal assay; OB: observer blinded; SB: single blind; MenC: meningococcal serogroup C; rSBA: rabbit serum bactericidal assay; OL: open label; Tdap: tetanus, diphtheria and pertussis vaccine; HPV: human papillomavirus vaccine; GMT: geometric mean titres;
Source: Compiled during the evaluation

Comparative effectiveness

Correlates of protection

6.10 The PBAC has previously accepted the use of serum bactericidal antibody (SBA) titres as a surrogate outcome for clinical efficacy in its consideration of the combined haemophilus influenzae type B and meningococcal C (Hib-MenC) vaccine (Menitorix), which used rabbit complement SBA (rSBA) titres > 1:8 to estimate vaccine efficacy. However, there is no established surrogate serological correlate of protection for non-MenC serogroups. Reliance on immunogenicity data increases uncertainty in the efficacy of the MenACWY-CRM vaccine against IMD caused by serogroups A, W and Y. The ESC noted that no clinical evidence was presented regarding vaccine efficacy against infection or disease caused by serogroups A, C, W or Y due to the relatively low incidence of IMD. Consequently, the submission presented immunogenicity results as a surrogate outcome that increases uncertainty regarding the clinical claim. The ESC noted this uncertainty applies to all MenACWY vaccine evaluations.

6.11 The PSCR reiterated that as most trials conducted with MenACWY-CRM vaccine reported human complement SBA (hSBA) titres that hSBA titres was appropriate for use as a correlate of protection. ATAGI advised (Pre-submission advice) that given the absence of data on rSBA titres, the following definition of 'vaccine response' was an acceptable correlate of protection in the short term: post-vaccination hSBA titre ≥1:8 in initially seronegative subjects, or ≥4-fold rise in the pre-vaccination hSBA titre in initially seropositive subjects (Pre-submission advice). This definition was used in the submission. The PSCR outlined the difficulty comparing SBA assays with different complement sources. The ESC noted the PSCR and the advice of ATAGI (Pre-submission advice) that meningococci are known to be more susceptible to complement-mediated lysis in the presence of exogenous rabbit complement comparted to human complement, and higher titres are expected with rSBA compared with hSBA. The ESC noted the difficulty in evaluation of conjugate vaccines where data is based on serological evidence in the form of serum bacterial activity as an immunological correlate of protection and not direct clinical evidence, the uncertainties associated with translating seroprotection into disease incidence and in comparing results reporting rSBA to those reporting hSBA.

6.12 In March 2018, the PBAC noted the lack of a surrogate serological correlate of protection for the efficacy of the MenACWY-TT vaccine against IMD caused by serogroups A, W and Y. The PBAC noted ATAGI's advice that 'vaccine response' is a reasonable measure of vaccine efficacy in the short term. The PBAC noted that vaccine response was used as a surrogate measure to inform efficacy in the economic model and that a better alternative measure was not available[7].

6.13 Tables 5 to 7 present the results of the clinical evidence.

[7] PBAC (*March 2018) Public summary document: Meningococcal polysaccharide conjugate vaccine serogroups A, C, W-135 and Y (adolescents), pre-filled syringe, 0.5mL, Nimenrix*

Seroresponse

6.14 Seroresponse was only reported by Study V59P13 and Study V59_39d.

6.15 The submission defined seroresponse as:

- For subjects with a prevaccination hSBA <1:4, a postvaccination hSBA titer ≥1:8; OR
- For subjects with a prevaccination hSBA ≥1:4, an increase in hSBA titer of at least four times the prevaccination titer.

6.16 Study V59P13: Seroresponse was achieved by 68% (MenY) to 76% (MenC) of subjects with MenACWY-CRM. The percentage of seroresponders was consistently higher in the MenACWY-CRM vaccine group than in the MenACWY-DT vaccine group for serogroups A, W and Y, while it was similar for serogroup C. Non-inferiority criteria[8] were met for all four serogroups, and superiority was met for all serogroups except C. The largest differences were observed for serogroup Y and W.

6.17 Study V59_39d: Seroresponse was achieved by 28% (MenW) to 86% (MenC) of subjects with MenACWY-CRM. The primary immunogenicity objective for MenW was not met.

SBA titres and Geometric mean titres (GMTs)

6.18 SBA titres and GMTs at 1 month post-vaccination were measured across all of the studies. Study V59P13, V59P6 and V59_39d reported hSBA titres, while the submission assumed that the study by Ishola reported rSBA titres.

6.19 The proportion of subjects with SBA-Men titres ≥ 1:8 with MenACWY-CRM for:

- Serogroup A ranged from 1% to 36% pre-vaccination and from 75% to 100% one month post-vaccination.
- Serogroup C ranged from 17% to 49% pre-vaccination and from 83% to 100% at one month post-vaccination.
- Serogroup W ranged from 13% to 89% pre-vaccination and from 90% to 100% at one month post-vaccination.
- Serogroup Y ranged from 11% to 54% pre-vaccination and from 88% to 98% at one month post-vaccination.

6.20 Many of the trial subjects were seropositive (hSBA-Men titres ≥ 1:8) prior to vaccination, which would increase the proportion of subjects who become seropositive after vaccination.

[8] Lower limit of the two-sided 95% CI around the difference in percentages of seroresponders (MenACWY-CRM (Menveo) minus MenACWY (Menactra)) is > -10%.

6.21 Ishola 2015: 100% of participants achieved SBA titres ≥ 1:8 against three serogroups for both MenACWY-CRM and MenACWY-TT, but 98% against MenY in those boosted with the MenACWY-CRM vaccine. These rates were higher than the other studies, likely due to subjects in Ishola 2015 receiving primary vaccination as children.

6.22 Ishola 2015: GMTs were higher with the MenACWY-CRM vaccine compared to the MenACWY-TT vaccine for MenA, MenC and MenY, but not for MenW. However, MenW and MenY antibodies did not differ significantly between the vaccine groups.

6.23 Other studies: GMTs were consistently higher with the MenACWY-CRM vaccine compared to the comparators across all four serogroups.

6.24 It is unclear whether the difference in magnitude of GMTs across the studies is due to different assays used across the trials.

6.25 ATAGI (Post-submission advice) advised that the additional studies provided in the submission did not use the same definition of vaccine response and noted the difference in GMT values across studies, further complicating any comparison across studies.

Table 5: Seroresponse at 1 month post-vaccination across the studies

Serogroup	Vaccine	Ishola 16-19 years (N=93) vs MenACWY-TT (Nimenrix) % (95% CI)		V59P13 11-18 years, MITT population (N=2180) vs MenACWY-DT (Menactra) n/N %			V59_39d 11-55 years, PP population, (N=450) vs Placebo n/N % (95% CI)		
		SBA[a]≥1:8	%≥4-fold	Baseline hSBA <1:4	Baseline hSBA ≥ 1:4	Overall seroresponse	Baseline hSBA <1:4	Baseline hSBA ≥ 1:4	Overall seroresponse
MenA	MenACWY-CRM	100% (92-100)	91% (79-98)	789/1054 75%	22/37 59%	811/1091 74%	187/246 76% (70-81)	37/49 76% (61-87)	224/295 76% (71-81)
	Comparator	100% (92-100)	91% (79-98)	232/351 66%	8/12 67%	240/363 66%	2/120 2% (0-6)	0/32 0% (0-11)	2//152 1% (0-5)
	Vaccine Group Difference (95% CI)[c]			9% (3-14)	-7% (-34-25)	8% (3-14)			
MenC	MenACWY-CRM	100% (92-100)	100% (92-100)	746/936 80%	323/476 68%	1069/1412 76%	107/111 96% (91-99)	146/182 80% (74-86)	253/293 86% (82-90)
	Comparator	100% (92-100)	98% (88-100)	238/301 79%	102/162 63%	340/463 73%	2/67 3% (0-10)	0/83 0% (0-4)	2/150 1% (0-5)
	Vaccine Group Difference (95% CI)[c]			1% (-4-6)	5% (-3-14)	2% (-2-7)			
MenW	MenACWY-CRM	100% (92-100)	98% (88-100)	578/617 94%	196/422 46%	774/1039 74%	27/32 84% (67-95)	54/261 21% (16-26)	81/293 28% (23-33)
	Comparator	100% (92-100)	100% (92-100)	153/183 84%	31/109 28%	184/292 63%	6/20 30% (12-54)	0/131 0% (0-3)	6/151 4% (1-8)
	Vaccine Group Difference (95% CI)[c]			10% (5-16)	18% (8-27)	11% (6-18)			
MenY	MenACWY-CRM	98% (88-100)	91% (79-98)	518/640 81%	195/412 47%	713/1052 68%	106/119 89% (82-94)	96/175 55% (47-62)	202/294 69% (63-74)
	Comparator	100% (92-100)	100% (92-100)	95/176 54%	28/122 23%	123/298 41%	3/62 5% (1-13)	0/90 0% (0-4)	3/152 2% (0-6)
	Vaccine Group Difference (95% CI)[c]			27% (19-35)	24% (15-33)	27% (20-33)			

CI: confidence interval; hSBA: human serum bactericidal assay; MenACWY-CRM: Meningococcal Oligosaccharide CRM197 Conjugate Vaccine; N = number of subjects; PP: per protocol.
a The SBA assay type is unknown. The submission claimed that it is likely to be rSBA, based on original study of Men C vaccine responses (p83 of the submission).
Source: Table 2.20 p73, Table 2.26 p81 and Table 2.28 p84 of the submission.

Table 6: Serogroup-Specific Serum Bactericidal Antibody (SBA) titers at 1 month across the studies

Sero-group	Vaccine	Ishola 16-19 years (N=93) vs MenACWY-TT (Nimenrix) % (95% CI)		V59P13 11-18 years, PP population (N=2180) vs MenACWY-DT (Menactra) n/N % (95% CI)		V59P6 11-17 years, MITT population (N=524) vs MenACWY (Menomune) n/N % (95% CI)				V59_39 11-55 years, PP population (N=450) vs Placebo n/N % (95% CI)	
		Preboost	1 Mo	Day 1	Day 29	Pre-vaccination		1 Mo		Day 1	Day 29
		SBA[a]≥1:8	SBA[a]≥1:8	hSBA≥1:8	hSBA ≥1:8	hSBA ≥ 1:4	hSBA ≥ 1:8	hSBA ≥ 1:4	hSBA ≥ 1:8	hSBA ≥ 1:8	hSBA ≥ 1:8
MenA	MenACWY-CRM	36% (23-51)	100% (92-100)	[redacted]	810/1075 75% (73-78)	2/148 1% (0-5)	2/148 1% (0-4)	124/148 84% (77-89)	120/148 81% (74-87)	[redacted]	[redacted]
	Comparator	30% (18-46)	100% (92-100)	[redacted]	240/359 67% (62-72)	5/179 3% (1-6)	1/179 1% (0.014-3)	82/179 46% (38-53)	74/179 41% (34-49)	[redacted]	[redacted]
	Vaccine Group Difference (95% CI)[c]			[redacted]	**8% (3-14%)**						
	P-value					-	-	***	***		
MenC[e]	MenACWY-CRM	49% (34-64)	100% (92-100)	[redacted]	1183/1396 85% (83-87)	36/148 24% (18-32)	25/148 17% (11-24)	130/148 88% (81-93)	123/148 83% (76-89)	[redacted]	[redacted]
	Comparator	30% (18-46)	100% (92-100)	[redacted]	390/460 85% (81-88)	48/177 27% (21-34)	32/177 18% (13-25)	126/177 71% (64-78)	112/177 63% (56-70)	[redacted]	[redacted]
	Vaccine Group Difference (95% CI)[c]			[redacted]	1%[b] (-4-4%)[d]						
	P-value					-	-	**	***		
MenW	MenACWY-CRM	15% (6-28)	100% (92-100)	[redacted]	983/1024 96% (95-97)	19/146 13% (8-20)	19/146 13% (8-20)	139/146 95% (90-98)	132/146 90% (84-95)	[redacted]	[redacted]
	Comparator	7% (1-18)	100% (92-100)	[redacted]	254/288 88% (84-92)	41/173 24% (18-31)	37/173 21% (16-28)	153/173 88% (83-93)	149/173 86% (80-91)	[redacted]	[redacted]
	Vaccine Group Difference (95% CI)[c]			[redacted]	**8% (4-12%)**						
	P-value					*	*	*	-		
MenY	MenACWY-CRM	11% (4-23)	98% (88-100)	[redacted]	908/1036 88% (85-90)	40/147 27% (20-35)	34/147 23% (17-31)	141/147 96% (91-98)	139/147 95% (90-98)	[redacted]	[redacted]
	Comparator	17% (8-31)	100% (92-100)	[redacted]	202/294 69% (63-74)	49/177 28% (21-35)	40/177 23% (17-29)	148/177 84% (77-89)	143/177 81% (74-86)	[redacted]	[redacted]
	Vaccine Group Difference (95% CI)[c]			[redacted]	**19% (14-25%)**						
	P-value					-	-	***	***		

CI: confidence interval; hSBA: human serum bactericidal assay; MenACWY-CRM: Meningococcal Oligosaccharide CRM197 Conjugate Vaccine; N = number of subjects; PP: per protocol.

a The SBA assay type is unknown. The submission claimed that it is likely to be rSBA, based on original study of Men C vaccine responses (p83 of the submission).

b Although both groups had a value of 84, there is a group difference of 1 because of rounding.

c Bold indicates superior. Superiority was determined if the lower limit of the 95% CI around the GMT ratio was >1 or if the lower limit of the 95% CI around the group difference was >0.

d Non-inferior. Non-inferiority was determined if the lower limit of the 95% CI around the GMT ratio was >0.5 or if the lower limit of the 95% CI around the group difference was >-10.

e Revised serogroup C titres for study V59P13. *P < .05, **P < .01, ***P < .001. Source: Table 2.21 p76, Table 2.23 p78, Table 2.27 p82 and Table 2.28 p84 of the submission.

Table 7: Geometric mean titers at one month across the studies

Sero-group	Vaccine	Ishola 16-19 years (N=93) vs MenACWY-TT (Nimenrix) GMT[a] (95% CI)			V59P13 11-18 years, PP population (N=2180) Vs MenACWY-DT (Menactra) GMT		V59P6 11-17 years, MITT population (N=524) vs MenACWY (Menomune) GMT (95% CI)			V59_39 11-55 years, PP population (N=450) vs Placebo GMT (95% CI)		
		Preboost	1 Mo		Day 1	Day 29	Prevaccination	1 Mo		Day 1	Day 29	
		GMT	GMT	GMR	GMT	GMT	GMT	GMT	GMR	GMT	GMT	GMR
MenA	MenACWY-CRM	19 (8-47)	10116 (7314-13992)	504	[redacted]	29	2.07 (1.99-2.16)	35 (26-44)	[redacted]	2.7 (2.47-2.95)	48 (39-57)	[redacted]
	Comparator	13 (6-30)	5706 (4003-8134)	440	[redacted]	18	2.07 (2-2.15)	6.97 (5.51-8.82)	[redacted]	2.86 (2.53-3.24)	[redacted]	[redacted]
	Vaccine Group Ratio (95% CI)[b]				[redacted]	**1.63 (1.31-2.02)**						
	P-value						-	***	***			
MenC	MenACWY-CRM	17 (9-35)	11585 (7560-17753)	735	[redacted]	50	3.19 (2.75-3.69)	58 (39-85)	[redacted]	7.82 (6.76-9.05)	231 (198-269)	[redacted]
	Comparator	7 (4-13)	8701 (6008-12601)	1209	[redacted]	41	3.24 (2.85-3.69)	30 (22-43)	[redacted]	5.94 (4.85-7.27)	[redacted]	[redacted]
	Vaccine Group Ratio (95% CI)[b]				[redacted]	**1.22 (0.97-1.55)**						
	P-value						-	*	**			
MenW	MenACWY-CRM	4 (2-6)	7597 (5586-10333)	2017	[redacted]	87	2.86 (2.32-3.51)	49 (39-62)	[redacted]	51 (44-61)	147 (125-171)	[redacted]
	Comparator	3 (2-4)	8967 (6733-11943)	3170	[redacted]	44	3.56 (2.96-4.29)	39 (24-37)	[redacted]	48 (38-60)	[redacted]	[redacted]
	Vaccine Group Ratio (95% CI)[b]				[redacted]	**2.00 (1.66-2.42)**						
	P-value						-	**	***			
MenY	MenACWY-CRM	5 (3-8)	4484 (3555-5655)	964	[redacted]	51	3.58 (3.02-4.26)	100 (75-133)	[redacted]	9.01 (7.64-11)	107 (89-128)	[redacted]
	Comparator	4 (2-7)	3915 (2390-6414)	1009	[redacted]	18	3.58 (3.07-4.17)	34 (27-44)	[redacted]	8.82 (7.02-11)	[redacted]	[redacted]
	Vaccine Group Ratio (95% CI)[b]				[redacted]	**2.82 (2.26-3.52)**						
	P-value						-	***	***			

CI: confidence interval; GMR: Geometric mean ratio; GMT: Geometric mean titers; MenACWY-CRM: Meningococcal Oligosaccharide CRM197 Conjugate Vaccine; N = number of subjects; PP: per protocol.
a The SBA assay type is unknown. The submission claimed that it is likely to be rSBA, based on original study of Men C vaccine responses (p83 of the submission).
b Bold indicates superior. Superiority was determined if the lower limit of the 95% CI around the GMT ratio was >1 or if the lower limit of the 95% CI around the group difference was >0.
*P < .05, **P < .01, ***P < .001.
Source: Table 2.22 p77, Table 2.25 p80, Table 2.27 p82 and Table 2.28 p84 of the submission.

Persistence

6.26 Vaccine efficacy persistence up to 5 years after vaccination was explored through follow-up of participants in Ishola 2015, and extension studies of V59P13 (V59P13E1) and V59PP6 (V59P6E1).

6.27 Overall vaccine efficacy declined over time across the persistence studies. ATAGI noted that the greatest decline in hSBA titres occurs in the first 2 years after receipt of MenACWY-CRM, followed by a period of relatively stable levels for 3-5 years (ATAGI pre-submission advice).

6.28 The ESC considered persistence beyond 5 years to be uncertain.

Concomitant administration

6.29 The submission also presented three studies comparing MenACWY-CRM administered concomitantly with a tetanus, diphtheria and pertussis vaccine (Tdap) and a HPV vaccine (V59P18, V59P11 and V59P4).

6.30 Study V59P18: ATAGI noted that the only identified interaction was minor reductions in geometric mean concentrations (GMCs) of FHA and PRN pertussis antigens, seen with concomitant vaccination against dTpa alone, but the proportion of recipients with ≥4-fold rise of at least 2 of 3 pertussis antigens were similar (86% concomitant group and 88% dTpa alone). Serogroup W responses (%hSBA≥1:8) were lower when MenACWY-CRM was administered 1 month after (65% [95% CI: 61-70]) rather than 1 month before dTpa (81% [95% CI: 77-84]) (ATAGI pre-submission advice).

6.31 Study V59P11: ATAGI noted that this trial showed similar findings with no interactions for tetanus or diphtheria responses, but non-inferiority shown only for FHA (but not PRN or PT) anti-pertussis antibodies (ATAGI pre-submission advice).

6.32 Study V59P40: ATAGI noted that this trial found no interaction between the MenACWY-CRM vaccine and anti-pertussis antibody GMCs (ATAGI pre-submission advice).

6.33 No studies were available assessing efficacy of MenACWY-CRM with a nine valent HPV (9vHPV) vaccine.

Naïve indirect comparison

6.34 Table 8 presents the results of the naïve indirect comparison, using the MenACWY-DT vaccine (Menactra) as the common comparator.

Table 8: Summary of vaccine efficacy results of the naive indirect comparison[9]

Serogroup	Study V59P13		Study MenACWY-TT-71		Study MenACWY-TT-052	
	MenACWY-CRM / MenACWY-DT (95% CI)	MenACWY-CRM minus MenACWY-DT (95% CI)	MenACWY-TT / MenACWY-DT (95% CI) †	MenACWY-TT minus MenACWY-DT (95% CI)	MenACWY-TT / MenACWY-DT (95% CI) †	MenACWY-TT minus MenACWY-DT (95% CI)
A						
% Seroresponse‡	-	9 [Should be 8] (3, 14)	-	6.01 (-1.45, 13.44)	-	-
% ≥ 1:8	-	8 (3, 14)	-	7.22 (0.51-13.93)	-	11.20 (3.87, 19.18)
GMT Ratio	1.63 (1.31, 2.02)	-	1.34 (0.97, 1.84)	-	1.57 (1.13, 2.17)	
C						
% Seroresponse‡		2 (-2, 7)	-	0.95 (-6.10, 8.00)	-	-
% ≥ 1:8	-	0 (-4, 4)	-	-2.22 (-5.23, 0.48)	-	-2.77 (-5.08, 0.40)
GMT ratio	1.22 (0.97, 1.55)	-	1.35 (0.92, 1.99)	-	2.07 (1.45, 2.95)	-
W						
% Seroresponse‡	-	12 [Should be 11] (6, 18)	-	6.95 (-0.76, 14.59)	-	-
% ≥ 1:8	-	8 (4, 12)	-	8.11 (2.79, 13.58)	-	15.93 [Should be 14.93] (8.24, 22.71)
GMT ratio	2.00 (1.66, 2.42)	-	1.60 (1.15, 2.23)	-	1.98 (1.40, 2.80)	-
Y						
% Seroresponse‡	-	27 (20, 33)	-	12.21 (4.17, 20.10)	-	-
% ≥ 1:8	-	19 (14, 25)	-	3.98 (1.01, 7.43)	-	13.40 (7.90, 20.10)
GMT Ratio	2.82 (2.26, 3.52)	-	1.54 (1.21, 1.97)	-	2.48 (1.86, 3.32)	-

† GMT ratios and CI adjusted for age strata and baseline titer
‡ Seroresponse/vaccine response not included from study MenACWT-TT-52 due to different definitions to the other studies
Source: Table 2.72, p142 of the submission

6.35 There were differences in the definition of seroresponse across the trials. Study MenACWY-TT-071 applied a more stringent definition of vaccine response than Study V59P13. This biased the results in favour of the MenACWY-CRM vaccine.

[9] The PSCR (P7) stated that in Table 8 the W seroresponse for MenACWY-CRM minus MENACWY-DT should be 12, as per Table 11.4.1.1-2 of the V59P13 original study report. However, the corrected results presented in Table 8 of the Commentary, and in this advice, are consistent with the revised seroresponse results presented in the submission in Table 2.20 (p73), which were based on Table 14.2.1.2.2 (CSR V59P13_transcription addendum, 17 Aug 2011).

6.36 The submission stated that "A (formal) indirect comparison of these studies is not presented as the GMT results indicate that though the immunogenicity is measured using hSBA, there appears to be a significant difference in the assays since the values reported in the Nimenrix studies for both [MenACWY-TT] Nimenrix and [MenACWY-DT] Menactra are significantly higher than the values reported in the [MenACWY-CRM] Menveo studies for [MenACWY-CRM] Menveo and [MenACWY-DT] Menactra. Interpretation of these results would therefore be problematic. Additionally, study MenACWY-TT-052 uses a different measure of seroresponse and the % ≥1:8 and GMT results are influenced by baseline GMT with higher baseline GMT increasing both results." The ESC noted the variation in responses based on the baseline titre, where a higher baseline titer led to lower responses post vaccine.

6.37 The PSCR stated that whilst not perfectly matched, the studies were considered comparable with respect to baseline demographics. The ESC considered that given the inconsistent correlation between hSBA and rSBA titres and GMT results, and the evidence provided appeared to vary in these measures, cross-trial comparisons was difficult and uncertain.

6.38 ATAGI (Post-submission advice) advised that correlation between hSBA and rSBA titres is inconsistent, and varies by age, vaccination status, meningococcal serogroup and laboratory and that the lack of standardisation leads to difficulties in the direct comparison of results not conducted as part of the same study, in the same laboratory, with the same complement and strain of meningococci. ATAGI summarised that immunogenicity results between different clinical trials cannot be directly compared given the multiple factors impacting outcomes.

Comparative harms

6.39 Table 9 presents a summary of relevant-harms across the trials presented by the submission.

6.40 ATAGI considered that no significant safety concerns have been raised in clinical trials of the MenACWY-CRM vaccine in adolescents (ATAGI pre-submission advice).

6.41 The ESC considered that there were no significant safety concerns with use of MenACWY-CRM.

Table 9: Summary of key adverse events in the randomised trials

Trial ID	MenACWY-CRM n with event/N (%)	Comparator n with event/N (%)	Vaccine Group difference (95%CI)
Ishola 2015, comparator = MenACWY-TT (Nimenrix)			
AEs	"Overall similar level of reactogenicity"		
SAEs	3/47 (6)	1/46 (2)	NR
Possibly probably vaccine related	0	0	NR
V59P13, comparator = MenACWY-DT vaccine (Menactra)			
Severe systemic reaction	[redacted]	[redacted]	1 (-1, 2)
Any reaction	[redacted]	[redacted]	NR
Any local reaction	[redacted]	[redacted]	NR
Any systemic reaction	[redacted]	[redacted]	NR
Any other reaction	[redacted]	[redacted]	NR
Any AE	[redacted]	[redacted]	NR
Possibly probably related AEs	[redacted]	[redacted]	NR
SAEs	[redacted]	[redacted]	NR
Possibly probably related SAEs	0	0	NR
Death	0	0	NR
V59P6, comparator = MenACWY vaccine (Menomune) (stage 1 and Stage 2)			
Any reaction	127/151 (84)	129/170 (76) and 31/39 (79)	NR
Any local reaction	107/151 (71)	102/170 (60) and 24/39 (62)	NR
Any systemic reaction	85/151 (56)	79/170 (46) and 23/39 (59)	NR
Any other reaction	40/151 (26)	45/170 (26) and 14/39 (36)	NR
Any AE	79/151 (52)	65/170 (38) and 17/39 (44)	NR
Possibly probably related AEs	10/151 (7)	4/170 (2) and 1/39 (3)	NR
SAE	2/151 (1)	5/170 (3) and 2/39 (5)	NR
Possibly probably related SAEs	0	0	NR
V59P39, comparator = placebo			
Any reaction	118/297 (40)	52/153 (34)	NR
Any local reaction	83/297 (28)	14/153 (9)	NR
Any systemic reaction	83/297 (28)	43/153 (28)	NR
Any other reaction	15/297 (5)	5/153 (3)	NR
Any AEs	36/297 (12)	10/153 (7)	NR
At least possibly related AEs	11/297 (4)	2/153 (1)	NR
Serious AEs	0	0	NR
Death	0	0	NR
V59P20E1, comparator = children not previously vaccinated with MenACWY-CRM			
Any reaction	39/64 (61)	59/98 (60)	NR
Any local reaction	34/64 (53)	49/98 (50)	NR
Any systemic reaction	19/64 (30)	35/98 (36)	NR
Any AEs	18/65 (28)	11/100 (11)	NR
Possibly related AEs	7/65 (11)	5/100 (5)	NR
SAE	0	0	NR
Deaths	0	0	NR
V59P18, MenACWY-CRM + Tdap + HPV vs sequentially or alone			
	MenACWY-CRM + Tdap + HPV	**MenACWY-CRM → Tdap → HPV**	**Tdap → MenACWY-CRM → HPV**
Any reaction (at visit 1)	481/540 (89)	373/541 (69)	444/539 (82)	NR
Any local reaction (at visit 1)	460/540 (85)	280/541 (52)	399/539 (74)	NR
Any systemic reaction (at visit 1)	312/540 (58)	274/541 (51)	309/539 (57)	NR
Any other reaction (at visit 1)	140/540 (26)	147/541 (27)	147/539 (27)	NR
Any AE (1 month after visit 1)	79/540 (15)	53/541 (10)	66/539 (12)	NR

Possibly probably related AEs (1 month after visit 1)	22/540 (4)	12/541 (2)	21/539 (4)	NR
SAEs (1 month after visit 1)	1/540 (<1)	0	0	NR
AEs leading to discontinuation (1 month after visit 1)	1/540 (<1)	0	0	NR
Possibly probably related SAEs (1 month after visit 1)	0	0	0	NR
V59P11, MenACWY-CRM + Tdap vs Tdap + saline vs MenACWY-CRM + saline				
	MenACWY-CRM + Tdap	**Tdap + saline**	**MenACWY-CRM + saline**	
Any reaction	263/313 (84)	277/315 (88)	206/316 (65)	NR
Local reaction	245/313 (78)	253/315 (80)	161/316 (51)	NR
Systemic reaction	178/313 (57)	183/315 (58)	150/316 (47)	NR
Other reaction	37/313 (12)	34/315 (11)	26/316 (8)	NR
Any AE	37/313 (12)	28/315 (9)	38/316 (12)	NR
Possibly probably related AE	8/313 (3)	5/315 (2)	6/316 (2)	NR
SAEs	0	0	0	NR
AEs leading to discontinuation	0	0	0	NR
Possibly probably related SAE	0	0	0	NR
Death	0	0	0	NR
V59P40 MenACWY-CRM + Tdap + HPV4 vs Tdap + placebo + HPV				
Any reaction	281/389 (72)	245/385 (64)		NR
Local reaction	209/389 (54)	164/385 (43)		NR
Systemic reaction	205/389 (53)	179/385 (46)		NR
Other reaction	88/389 (23)	80/385 (21)		
Any AEs	201/396 (51)	197/397 (50)		NR
At least possibly related AEs	[redacted]	[redacted]		NR
Serious AEs	4/396 (1)	3/397 (1)		NR
At least possibly related serious AEs	0	0		NR
AEs leading to premature withdrawal	2/396 (<1)[a]	0		NR
New onset of chronic disease	25/396 (6)	27/397 (7)		NR
Death	0	0		NR

AE: adverse event; HPV: human papilloma virus; MenACWY-CRM: Meningococcal Oligosaccharide CRM197 Conjugate Vaccine; NR: not reported; SAE: serious adverse event; Tdap: tetanus diphtheria acellular pertussis

Source: CSR V59P13 Table 2-4 2-5 and 2-6 p93, CSR V59P6 Table 12.2.3.6-1, p100, CSR V59P40 Table 2-3 and 2-4 p27, and Table 2.52 p113, Table 2.53 and Table 2.54 p114, and 2.55 p115, Table 2.57 and Table 2.58 p117, Table 2.60 p121, Table 2.61 p122, Table 2.62 and 2.63 p123, and Table 2.64 p124 of the submission.

Benefits and harms

6.42 The only trial comparing the MenACWY-CRM and MenACWY-TT vaccines directly (Ishola 2015) reported immunogenicity results only. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.43 The submission claimed that "there is no evidence of a difference in the immunogenicity or safety" between the MenACWY-CRM vaccine (Menveo) and the MenACWY-TT vaccine (Nimenrix).

6.44 The submission also claimed that:

- "The MenACWY-CRM vaccine is immunogenic in the adolescent age group (average age 15 years) against the four N. meningitidis serogroups A, C, W and Y;
- The MenACWY-CRM vaccine may be co-administered with routine vaccinations given to adolescents within the NIP;
- Adolescent subjects vaccinated with a single dose of the MenACWY-CRM vaccine demonstrated a sustained immune response up to 5 years post vaccination; and
- The MenACWY-CRM vaccine is well tolerated, with an acceptable safety profile."

6.45 The evaluation and the ESC considered that the claim that the MenACWY-CRM vaccine is immunogenic is reasonable. However, the evaluation noted the therapeutic claim regarding the relative vaccine efficacy of the MenACWY-CRM vaccine compared to the MenACWY-TT vaccine was not adequately supported by the evidence presented in Section 2 of the submission because:

- None of the trials collected clinical efficacy data in terms of cases of MenACWY avoided. Immunogenicity does not necessarily correlate to efficacy of a vaccine to prevent a disease. Given meningococcal disease is relatively rare, evidence of efficacy would be difficult. The ESC noted this uncertainty applies to all MenACWY vaccine evaluations.
- Comparison of the MenACWY-CRM to the MenACWY-TT vaccine was based on limited data. Only one direct RCT (Ishola 2015) was presented, along with a naive indirect comparison of studies.
    - It is unclear whether the study by Ishola 2015 was blinded. It did not report the proportion achieving seroresponse as defined for this submission. The study was small (N=93) and not powered to test for non-inferiority between the vaccines. The PSCR acknowledged that blinding status was unknown, stating that subjects were randomised via a computer-generated list and that seroresponse outcomes, the main outcomes of the study, are not subject to bias. The PSCR added that Ishola 2015 sought a sample size of 50 in each group and the resulting sample size of 93 was very close to that planned. The PSCR also added that the trial was highly applicable to the Australian context as subjects received a MenC vaccine as infants/children. The ESC considered that although the trial estimated the percentages of subjects achieving protective antibody levels, the trial was not powered to assess non-inferiority of the two vaccines.
    - The naïve indirect comparison was limited due to 1) differences in the trial design, including the definition of seroresponse; 2) differences in the assays used in the trials to measure immunogenicity; 3) differences in baseline pre-vaccination protection; and 4) a lack of a formal indirect comparison. The PSCR reiterated that indirect comparison was not presented due to the difference in

GMTs reported in two of the studies, and the informal comparison was supportive of Ishola 2015. The ESC noted the uncertainties with cross-trial comparisons using different complement assay types, the different definitions of seroresponse across trials and differences in baseline protection and agreed that that the assessment of comparative vaccine effectiveness was uncertain.

6.46 Overall, the ESC considered it is uncertain whether the vaccine efficacy between the MenACWY-CRM vaccine and the MenACWY-TT vaccine is of a similar magnitude. The ESC noted, however it is unlikely that additional data would become available to address this uncertainty, and noted that MenACWY-CRM is one of a number of vaccines used in State-based programs.

6.47 The ESC considered the therapeutic conclusion that MenACWY-CRM is well tolerated, with an acceptable safety profile is likely reasonable, although ESC noted limited safety reporting by the study by Ishola 2015. The PSCR reiterated that the MenACWY-CRM studies consistently showed that the vaccine was safe and well tolerated.

6.48 The PBAC considered that the claim that there is no evidence of a difference in the immunogenicity or safety between the MenACWY-CRM and MenACWY-TT vaccines was reasonable.

Economic analysis

6.49 The submission proposed a price for the MenACWY-CRM vaccine equivalent to the nationally negotiated price of the MenC component of the Hib-MenC vaccine listed on the NIP for use in infants ($[redacted]), a different population.

6.50 The submission stated that "If either Nimenrix or Menveo is recommended in an adolescent population at the March or July 2018 PBAC meetings, respectively, it is anticipated that the price will be the same as in the infant population, and therefore $[redacted] represents an appropriate price for Menveo in this economic evaluation". The ESC noted that the price of MenACWY-CRM would be informed by the MenACWY-TT PBAC recommendation for adolescents, not the infant dose of MenACWY-TT, as the adolescent dose reflects the same population group.

6.51 The positive PBAC recommendation for the NIP listing of the MenACWY-TT vaccine for the adolescent population is yet to be implemented and is contingent upon the sponsor of MenACWY-TT accepting a price reduction such that the incremental cost-effectiveness ratio is less than $15,000 per quality adjusted life year (QALY) gained[10]. The sponsor noted in the PSCR that if MenACWY-TT vaccine were listed, acceptance of the agreed price for MenACWY-TT would be required for the listing of MenACWY-

[10] PBAC (March 2018) Public summary document: Meningococcal polysaccharide conjugate vaccine serogroups A, C, W-135 and Y (adolescents), pre-filled syringe, 0.5mL, Nimenrix

CRM. The PSCR stated that the PBAC should be aware the low vaccine prices could impact supply where there is international competition or limited doses, which may reduce confidence in the NIP. The Pre-PBAC Response stated that a low recommended price may impact the sponsor's ability to progress listing and requested that "the PBAC consider the limitations on vaccine supply due to complex manufacturing processes and associated long lead times, and existing issues with supply constraints of multiple brands of MenACWY vaccine due to high global demand."

6.52 The ESC noted that the submission did not present a cost-effectiveness analysis compared with 'no vaccine' (placebo) and hence the only basis for listing was a cost-minimisation analysis versus MenACWY-TT.

Drug cost/patient/course

6.53 $[redacted], based on a single dose per adolescent.

Estimated PBS usage & financial implications

6.54 This submission was not considered by DUSC. The submission used an epidemiology approach to estimate the MenACWY-CRM vaccine usage and financial implications for the routine and catch-up program.

6.55 Key sources of data used were ABS population projections for Australian adolescents aged 15-19 years. The submission estimated the uptake rate of the routine program based on uptake of the human papilloma virus (HPV) vaccination program and of the catch-up program based on a MenW vaccine in England. The evaluation considered that the uptake rates are uncertain. The PSCR stated that uptake was based on the best available information in the absence of local data.

6.56 The submission estimated the cost of the catch-up program for Year 1 (2019) only. The submission excluded students who received a MenACWY vaccine through the State-based programs based on the sponsor's tender data when estimating the number of MenACWY-CRM vaccines in the catch-up program. Uptake of the catch-up program was based on a MenW vaccine program in England.

6.57 The estimated use and financial implications of the routine and catch-up vaccination programs are presented in Table 10.

Table 10: Estimated use and financial implications

	2019	2020	2021	2022	2023	2024
Estimated extent of use						
Estimated number of adolescents aged 15 years likely to receive MenACWY-CRM.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated number of adolescents aged 15 years require an additional dose likely to receive MenACWY-CRM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated number of MenACWY-CRM doses dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients electing treatment via school-program (83.80%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients electing treatment via GP (16.20%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Catch-up program						
Estimated number of adolescents aged 16-19 years catch-up population likely to receive MenACWY-CRM	[redacted]	0	0	0	0	0
Estimated number of adolescents aged 16-19 years require an additional dose likely to receive MenACWY-CRM	[redacted]	0	0	0	0	0
Estimated number of MenACWY-CRM doses dispensed	[redacted]	**0**	**0**	**0**	**0**	**0**
Patients electing treatment via school-program (83.80%)	[redacted]	0	0	0	0	0
Patients electing treatment via GP (16.20%)	[redacted]	0	0	0	0	0
Estimated financial implications to NIP						
Cost to NIP (routine program)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to NIP (routine program) (addition dose for at-risk group)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to NIP (catch-up program)	$[redacted]	$0	$0	$0	$0	$0
Cost to NIP (catch-up program) (addition dose for at-risk group)	$[redacted]	$0	$0	$0	$0	$0
Net cost to NIP	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
Copayments	$0	$0	$0	$0	$0	$0
Estimated financial implications to MBS						
Cost to MBS (routine program)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to MBS (routine program) (addition dose for at-risk group)	$[redacted] ($[redacted])	$[redacted] ($[redacted])	$[redacted] ($[redacted])	$[redacted] ($[redacted])	$[redacted] ($[redacted])	$[redacted] ($[redacted])
Cost to MBS (catch-up program)	$[redacted]	$0	$0	$0	$0	$0
Cost to MBS (catch-up program) (addition dose for at-risk group)	$[redacted]	$0	$0	$0	$0	$0
Net cost to MBS	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
Copayments	$0	$0	$0	$0	$0	$0
Net financial implications						
Net cost to the Australian Government health budget	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

NIP: National Immunisation Program, GP: general practitioner

Source: compiled during the evaluation based on Section 4 Worksheet and Table 4.8, p169 of the submission, Table 4.9, p171 of the submission Table 4.5.3, p216 of the submission.

6.58 At year 5, the estimated number of doses of MenACWY-CRM vaccine administered was over 200,000 and the net cost to the NIP would be less than $10 million. At year 1, which included the proposed catch-up program, the estimated number of doses of MenACWY-CRM vaccine administered was over 200,000 and the net cost to the NIP would be $10 – $20 million. These estimates included the cost of the additional dose administered to at-risk groups.

6.59 The uptake rates are uncertain.

6.60 The evaluation questioned whether a booster would be required if the MenACWY-CRM vaccine is found to have poor persistence, such that it does not cover the full 15-24 year old time span. The PSCR stated that the persistence data suggested maintenance of effect for at least 5 years and stated that the need for a booster should also consider the need for direct protection as identified by burden of disease. The ESC noted that in the United States MenACWY is given to adolescents at 11-12 years of age with a booster recommended at 16 years[11]. The Australian Immunisation Handbook also recommends that the at-risk patient population receive a booster dose every 5 years after the previous dose of MenACWY. The submission did not include a request for these booster doses.

Quality Use of Medicines

6.61 The submission did not present any concerns in relation to the quality use of medicine.

6.62 ATAGI noted that considerable health professional and consumer education is required given that this is a new vaccine to be listed on the NIP. Additionally, significant public communication strategies would be required to make adolescents who have left school, or otherwise missed the school dose, aware of the need for and availability of vaccination in order to achieve good coverage (ATAGI pre-submission advice 2018).

6.63 Concerns requiring addressing via health professional and parent education should include:

- Difference between the current MenC vaccine and the MenACWY-CRM vaccine;
- Targeted education programs for Aboriginal and Torres Strait Islander populations – including health workers, health professionals, community elders and community members.

6.64 ATAGI recommended a review of the MenACWY-CRM vaccination program 5 years after implementation (ATAGI pre-submission advice 2018). This would help inform

[11] Centers for Disease Control and Prevention, CDD Features – Meningococcal vaccines for preteens, teens, https://www.cdc.gov/features/meningococcal/index.html, accessed June 2018

whether a booster is required if the MenACWY-CRM vaccine is found to have poor persistence, such that it does not cover the full 15-24 year old time span.

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

7 PBAC Outcome

7.1 The PBAC recommended that meningococcal serogroups A, C, W135 and Y oligosaccharides conjugate (MenACWY-CRM, Menveo®) vaccine be a designated vaccine for the purposes of the Act for the prevention of IMD caused by Neisseria meningitidis serogroups A, C, W135, and Y (MenA, MenC, MenW135 and MenY, respectively) as a single dose for adolescents as part of a school based immunisation program for year 10 students (aged 14-16) and via a catch-up program for a single dose for adolescents aged up to 19 years old. The recommendation was made on a cost-minimisation basis to meningococcal polysaccharide serogroups A, C, W135 and Y tetanus toxoid conjugate vaccine (MenACWY-TT, Nimenrix®), with equi-effective doses of 0.5 mL MenACWY-CRM and 0.5mL MenACWY-TT.

7.2 The PBAC recalled it recommended MenACWY-TT vaccine be listed on the NIP for adolescents in March 2018. The PBAC further recalled that it recommended MenACWY-TT on a cost-effectiveness basis, subject to a reduction in the requested price such that the cost per QALY gained was less than $15,000.[12] The PBAC noted that this recommendation is yet to be implemented. The PBAC further noted that the sponsor of MenACWY-CRM chose not to present a cost-effectiveness analysis compared with 'no vaccine' (placebo) in this submission; accordingly, the basis of the recommendation for MenACWY-CRM for adolescents is cost-minimisation with MenACWY-TT for the same population.

7.3 The PBAC noted that currently there are several State-based meningococcal programs for the provision of MenACWY vaccines (including MenACWY-TT and MenACWY-CRM) with varied inclusion criteria and coverage.

7.4 The PBAC reaffirmed from its March 2018 recommendation for MenACWY-TT vaccine that there was a clinical need for the vaccination of the adolescent age group to both provide direct protection and to provide indirect protection to other age groups through herd immunity. The PBAC noted the increase in MenW and Y cases in recent years, and that a decrease in incidence of C strain was seen after the introduction of the meningococcal C vaccine. However, the PBAC considered that the impact of a MenACWY vaccination program is unknown due to uncertain vaccine effectiveness and unpredictability of the natural epidemiology of meningococcal disease.

[12] PBAC (2018) March 2018 - Positive Recommendations

7.5 The PBAC recommended that the listing for MenACWY-CRM be consistent with the March 2018 recommended listing for MenACWY-TT. Accordingly, NIP listing was recommended for adolescents aged 14 to 16 years old, in year 10 and for a catch-up program for students in year 11 and 12 or school leavers.

7.6 The PBAC noted that the submission also requested an additional vaccine dose in adolescents at increased risk of IMD. The PBAC noted that this was inconsistent with the recommended listing of MenACWY-TT, which did not include an additional dose in this sub-group, and that the sub-group of adolescents at increased risk of IMD did not appear to be represented within the clinical trials. The PBAC considered that there may be a clinical need for an additional dose of quadrivalent meningococcal vaccine for those at greatly increased risk of IMD across all age groups and welcomed a major submission for NIP listing presenting evidence that this would be clinically and cost effective for these populations.

7.7 The submission did not propose a main comparator; rather it nominated MenACWY-TT (Nimenrix®) and MenACWY-DT (Menactra®) vaccines as near-market comparators. The PBAC considered that MenACWY-TT was an appropriate comparator, noting the positive recommendation for adolescents in March 2018. The PBAC agreed that other MenACWY vaccines currently distributed through State-based programs were also relevant near-market comparators.

7.8 The PBAC noted the results of the clinical evidence provided, the naïve indirect comparison, the use of different assays across trials and the persistence data. The PBAC noted the limitations of the available clinical evidence including a small RCT study directly comparing MenACWY-CRM to the comparator MenACWY-TT, and a naïve indirect comparison using other studies and the limitations around the evidence on persistence.

7.9 The PBAC considered the clinical claim of no difference in the immunogenicity between the MenACWY-CRM and MenACWY-TT was reasonable.

7.10 The PBAC recalled that for MenACWY-TT there was uncertainty around the level of benefit provided by vaccination due to the lack of a surrogate serological correlate of protection for the efficacy of the MenACWY-TT vaccine against IMD caused by serogroups A, W and Y; the impact of vaccination on herd immunity in other age groups in the Australian context; the natural history of the disease and likely future burden of disease without vaccination; and the costs associated with treating the permanent sequelae of IMD. The PBAC considered that these uncertainties also applied to MenACWY-CRM. The PBAC noted that it is unlikely that additional data would become available to address these uncertainties and that both MenACWY-CRM and MenACWY-TT are currently used in State-based programs.

7.11 The PBAC considered that the claim that there is no evidence of a difference in safety between the MenACWY-CRM and MenACWY-TT vaccines was reasonable and noted that adverse events associated with these vaccines are generally mild or

moderate. The PBAC noted that MenACWY-CRM has been used in State-based vaccination programs without any concerns of safety emerging.

7.12 The PBAC noted that the utilisation and financial estimates were uncertain due to the submission only costing the first year of the catch-up program and uncertain uptake rates of the current State-based programs and the proposed NIP program.

7.13 The PBAC noted that ATAGI recommended a review of this drug five years after implementation and that activities to support quality use of this medicine were suggested.

7.14 The PBAC noted that this submission is not eligible for independent review as independent review is only relevant to PBS listing.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item to the NIP:

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Proprietary name and manufacturer
Meningococcal (Groups A, C, W-135 and Y) Oligosaccharide CRM197 Conjugate Vaccine powder and solvent for solution for injection Pre-filled syringe, 0.5mL	1	1	0	Menveo®, GlaxoSmithKline Australia Pty Ltd
Category/Program – NIP Routine NIP indication: • A single dose of Menveo (MenACWY-CRM) for adolescents aged 14 to 16 years old (administered via a school-based program * OR • A single dose of Menveo (MenACWY-CRM) for adolescents aged up to 19 years administered via a school-based catch-up program or accessed via the GP (school-leavers).** * For all adolescents in year 10. ** For all adolescents in year 11 and 12 (or school-leavers)-who did not receive the vaccination in year 10.				

9 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.

10 Sponsor's Comment

GSK welcomes the PBAC positive recommendation for inclusion of Menveo on the NIP for year 10 students (aged 14-16). GSK looks forward to working with the PBAC to ensure the recommendation can be implemented.