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# PHARMACEUTICAL SCHEDULE APPLICATION

**To:** PTAC

**From:** Therapeutic Group Manager - Vaccines

**Date:** January 2019

## Meningococcal ACWY vaccination eligibility

| SUMMARY OF PHARMACEUTICAL | | | |
|---|---|---|---|
| **Brand Name** | Menactra | **Chemical Name** | Meningococcal (Groups A,C,Y and W) conjugate vaccine |
| **Indications** | Prophylaxis | **Presentation** | Injection |
| **Therapeutic Group** | Vaccines | **Dosage** | |
| **Supplier** | Sanofi-Aventis New Zealand Limited | **Application Date** | NA |
| **MOH Restrictions** | Prescription medicine | **Proposal type** | Access widening |
| **Current Subsidy** | $89.95 per dose Menactra (Manufacturer's price, confidential net price applies) | | |
| **Proposed Subsidy** | TBC following RFP | **Manufacturer's Surcharge** | Nil |

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# QUESTIONS TO PTAC

*Note to PTAC members: These questions have been identified by PHARMAC staff as being particularly relevant to the application. Please feel free to provide additional information as appropriate.*

## Need

1. Does meningococcal disease disproportionally affect:
    - Māori?
    - Pacific people?
    - Other groups already experiencing health disparities relative to the wider New Zealand population (eg. NZ Dep 9-10 deprivation, refugees/asylum seekers)?
2. What is the strength and quality of evidence in relation to health needs due to meningococcal disease?

*Note to Committee: further questions relating to the group sizes will be included in the late paper about meningococcal ACWY costs.*

## Health benefit

3. Does meningococcal ACWY vaccine provide any additional health benefit or create any additional risks compared with other funded treatment options? If so, what benefits or risks are different from alternative treatments?
4. Which patient population would benefit most from meningococcal ACWY vaccine?
5. What is the strength and quality of evidence, including its relevance to NZ, for health benefits that may be gained from meningococcal ACWY vaccine?
6. Would meningococcal ACWY vaccine produce a health benefit for family, whānau or wider society, additional to the health benefits for people at risk of meningococcal disease? If so how, and what is the strength and quality of evidence for this benefit?
7. Should meningococcal ACWY criteria be widened, are there any consequences to the health system that have not been noted in the application?

## Suitability

8. Are there any non-clinical features of the meningococcal ACWY vaccine formulation that may impact on use, either by the patient, by family, or by healthcare workers, that have not been considered in the application?

## Costs and savings

*Note to Committee: further questions related to costs and savings will be included in the late paper about meningococcal ACWY costs.*

## Recommendations

9. Should meningococcal ACWY vaccine be listed in the Pharmaceutical Schedule for adolescents in close living situations?
    9.1. If listing is recommended, does the Committee recommend a catch-up programme? If so, how long should the catch-up period be?

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9.2. If listing is recommended, how does the Committee define the eligible group, and which vaccine is recommended?

9.3. If listing for adolescents in close living situations is recommended, what priority rating would you give to this proposal? **[low / medium / high / only if cost-neutral]**?

10. Should meningococcal ACWY vaccine be listed in the Pharmaceutical Schedule for a universal adolescent dose?

10.1. If listing is recommended, does the Committee recommend a catch-up programme? If so, how long should the catch-up period be?

10.2. If listing for a universal adolescent dose is recommended, what priority rating would you give to this proposal? **[low / medium / high / only if cost-neutral]**?

11. Should meningococcal ACWY vaccine be listed in the Pharmaceutical Schedule for children aged 1 to 4 years?

11.1. If listing is recommended, does the Subcommittee recommend a catch-up programme?

11.2. If listing for children aged 1 to 4 years is recommended, what priority rating would you give to this proposal? **[low / medium / high / only if cost-neutral]**?

12. Does the Committee have any recommendations additional to the application?

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## PURPOSE OF THIS PAPER

The purpose of this paper is to seek advice from the Committee regarding the funding of meningococcal ACWY (Men ACWY) quadrivalent vaccine for people in close living situations and universal childhood vaccination of infants, toddlers and teenagers.

## DISCUSSION

### BACKGROUND

In February 2014, the Immunisation Subcommittee considered a paper initiated by PHARMAC staff about meningococcal C vaccine eligibility (Subcommittee minutes in Appendix 1). The Subcommittee deferred making a recommendation on widening access to meningococcal C vaccines, instead recommending that PHARMAC staff assess the effects of funding a meningococcal C vaccination programme for people in close living situations such as prisons, barracks, university halls of residence and those boarding at boarding schools, as well as for universal vaccination of infants and adolescents or teenagers, particularly instituted with a catch-up programme.

In May 2018, the Subcommittee considered a paper from PHARMAC staff assessing the effects of funding a meningococcal C vaccination programme for people in close living situations as well as universal vaccination of infants and adolescents or teenagers, with a catch-up programme. The Subcommittee requested that PHARMAC staff further refine the group size for people in close living situations and provide the most recent meningococcal C epidemiology possible (Immunisation Subcommittee minutes in Appendix 2).

At its meeting in September 2018, the Immunisation Subcommittee considered a paper from PHARMAC staff with updated epidemiology for meningococcal disease and estimated costs of various population options for people in close living situations and universal childhood vaccination of infants, toddlers and teenagers. The Subcommittee recommended that a quadrivalent meningococcal vaccine be listed for toddlers in the second year of life and adolescents with possible catch-up, with a high priority. The Subcommittee considered that it should review toddler dosing and possible catch-up options following the close of the planned commercial process. The Subcommittee recommended that meningococcal C vaccine for universal vaccination be declined (Subcommittee minutes in Appendix 3).

In November 2018, PHARMAC issued an RFP for the supply of vaccines from July 2020. The RFP included an option for possible meningococcal vaccination programmes with Men ACWY and Men B vaccines. The costs and cost effectiveness of meningococcal programmes will be considered by PTAC as a late paper, to be written following the close of the RFP in January 2019.

In November 2018 the Ministry of Health declared an outbreak of MenW in the Northland region. The Ministry's Technical Advisory Group (TAG), which was comprised of members of the Immunisation Subcommittee, recommended that an outbreak be declared in Northland and that a vaccination response with a quadrivalent vaccine was appropriate. PHARMAC approved the funding and purchased 20,650 doses of Menactra for children aged 9 months to 4 years and adolescents aged 14-19 years of age. Subsequently, at the request of Northland DHB an additional 5,000 doses of Nimenrix quadrivalent meningococcal vaccine were obtained to cover a possible delay in the final delivery of Menactra. The outbreak supply was

not listed in the Pharmaceutical Schedule but provided directly to Northland DHB under specific distribution arrangements for the programme. The programme was planned to be delivered through special community vaccination clinics and a secondary school programme. The TAG also considered that although the Northland outbreak was the priority, consideration should be given to a national MenACWY programme to reduce the spread of group W disease prior to any potential changes to the immunisation schedule in 2020. Immunisation Subcommittee members gave advice by email that they agreed with the TAG recommendations regarding the outbreak response and consideration of a possible national MenACWY programme.

## Need

### Description of the disease

Meningococcal disease is caused by *Neisseria meningitidis*, a gram-negative bacterium, and is an important cause of sepsis and meningitis. Worldwide, the most important serogroups of meningococci are groups A, B, C, W and Y. Transmission from person to person is by respiratory droplets or direct contact with nasopharyngeal secretions, from a carrier or case. Historically, the incidence of meningococcal disease in NZ has been predominantly caused by meningococcal serogroups B and C, although W and Y have increased in recent years. Groups W and Y have accounted for more cases than C since 2017. Mortality and morbidity associated with meningococcal C and W is higher than that associated with meningococcal B.

In 2018, 113 cases of meningococcal disease were notified in New Zealand, which was higher than the 105 cases in 2017 and continues an increasing trend since the low of 36 cases reported in 2014. However, the number of cases in 2018 remains significantly lower than the 647 cases in 2001 during the meningococcal disease epidemic (driven by the B:P1.7-2,4 strain) (ESR report available online: https://surv.esr.cri.nz/PDF_surveillance/AnnualRpt/AnnualSurv/2016/NotifiableDiseaseReportCommentary2016.pdf). Group B strains continued to be the most prevalent and are discussed in the Meningococcal B paper. In 2018, 55% of identified cases were for non-B disease, with Group W being the most prevalent of the non-B groups. Group prevalence is described in Table 1 below:

*Table 1: Meningococcal disease cases by group by year, 2013-2018*

| Strain group | Year | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019** |
| **Group B** | **30** | **26** | **41** | **47** | **70** | **51** | **2** |
| B:P1.7-2,4 | 11 | 13 | 10 | 23 | 27 | 16 | 1 |
| Other group Bs | 19 | 13 | 31 | 24 | 43 | 35 | 1 |
| **Group C** | **17** | **6** | **6** | **8** | **11** | **10** | **2** |
| C:P1.5-1,10-8 | 15 | 5 | 3 | 4 | 8 | 6 | 2 |
| Other group Cs | 2 | 1 | 3 | 4 | 3 | 4 | 0 |

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| **Other** | **11** | **4** | **12** | **12** | **24** | **52** | **0** |
|---|---|---|---|---|---|---|---|
| Group W | 5 | 0 | 6 | 5 | 12 | 33 | 0 |
| Group Y | 4 | 3 | 6 | 7 | 11 | 16 | 0 |
| Group E | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Group X | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Non-groupable | 2 | 0 | 0 | 0 | 1 | 2 | 0 |

*2017-2019 data as of 15 Jan 2019
**2019 data from 1-15 Jan 2019 only
Source: ESR

In 2017 and 2018 there have been more cases of groups W and Y than of B. These cases have tended to be more predominant in those 20 years of age or older, however these groups have high morbidity and mortality in those under one year of age. The number of cases of all groups by age group are shown in Table 2:

*Table 2. Number of meningococcal disease cases by strain group 2017 and 2018*

**2017**

| Strain group | Age group | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | <1 | 1 to 4 | 5 to 9 | 10 to 14 | 15 to 19 | 20+ | |
| **Group B** | **12** | **17** | **4** | **1** | **10** | **26** | **70** |
| B:P1.7-2,4 | 2 | 4 | 1 | 0 | 6 | 14 | 27 |
| Other group Bs | 10 | 13 | 3 | 1 | 4 | 12 | 43 |
| **Group C** | **1** | **2** | **1** | **0** | **4** | **3** | **11** |
| C:P1.5-1,10-8 | 1 | 0 | 1 | 0 | 4 | 2 | 8 |
| Other group Cs | 0 | 2 | 0 | 0 | 0 | 1 | 3 |
| **Other** | **1** | **2** | **0** | **2** | **1** | **18** | **24** |
| Group W | 1 | 0 | 0 | 1 | 1 | 9 | 12 |
| Group Y | 0 | 2 | 0 | 1 | 0 | 8 | 11 |
| Non-groupable | 0 | 0 | 0 | 0 | 0 | 1 | 1 |

**2018**

| Strain group | Age group | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | <1 | 1 to 4 | 5 to 9 | 10 to 14 | 15 to 19 | 20+ | |
| **Group B** | **11** | **7** | **3** | **3** | **12** | **15** | **51** |
| B:P1.7-2,4 | 1 | 1 | 0 | 0 | 5 | 9 | 16 |
| Other group Bs | 10 | 6 | 3 | 3 | 7 | 6 | 35 |
| **Group C** | **1** | **1** | **0** | **1** | **2** | **5** | **10** |
| C:P1.5-1,10-8 | 1 | 1 | 0 | 0 | 1 | 3 | 6 |
| Other group Cs | 0 | 0 | 0 | 1 | 1 | 2 | 4 |
| **Other** | **4** | **5** | **5** | **1** | **4** | **33** | **52** |
| Group W | 3 | 4 | 3 | 1 | 3 | 19 | 33 |
| Group Y | 1 | 1 | 1 | 0 | 0 | 13 | 16 |
| Group X | 0 | 0 | 0 | 0 | 0 | 1 | 1 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Non-groupable | 0 | 0 | 1 | 0 | 1 | 0 | 2 |

The rising group W disease is similar to the experience in Australia, where W became the predominant group in 2016 (109/253 cases, 43%). While most group W cases in Australia have been reported in adults, there has been an increase in cases in children aged less than 5 years. Many of the group W cases belong to a hypervirulent sequence type (ST-11), associated with a higher risk of invasive disease and a higher case fatality rate. A similar increase in group W cases has also been reported in the United Kingdom (210 cases in 2015/16) (ESR 2016 Annual Surveillance report).

**The availability and suitability of existing medicines, medical devices and treatments**

Meningococcal ACWY vaccine (Menactra) is currently not universally funded under the National Immunisation Schedule. Since 2014, Menactra has been funded for small sub-populations of patients considered to be high-risk.

Up to three doses and a booster every 5 years are funded for patients pre- and post-splenectomy and those with functional or anatomic asplenia, HIV, complement deficiency (acquired or inherited), or pre- or post-solid organ transplant; one dose for close contacts of meningococcal cases; and two doses for bone marrow transplant patients and for patients following immunosuppression (due to steroids or other immunosuppressive therapy must be for a period of greater than 28 days).

Children under seven years of age require 2 doses 8 weeks apart, a booster dose three years after primary series and then five yearly.

*Note: PHARMAC is currently reviewing vaccine criteria regarding immunosuppression to ensure criteria refer to pre-elective immunosuppression lasting longer than 28 days as well as following immunosuppression (Immunisation Subcommittee recommendation October 2016). PHARMAC is also reviewing the vaccine criteria to include patients who have been infected with meningococcal bacteria (Immunisation Subcommittee recommendation July 2017).*

PHARMAC data summarising the distribution of the Menactra vaccination in the last 5 years is provided in the table below, indicating a small, but not insignificant (and growing) population.

| FYR | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|
| Menactra | 1004 | 1566 | 1782 | 2112 |

**The health need of family, whānau, and wider society**

Should a child contract meningococcal disease, an adult would need to provide care. Many of the sequelae of meningococcal infection would be likely to create a burden on caregivers, to the point that they reduce the health-related quality of life of family and whānau. The parent or caregiver are also at risk of contracting the disease and it may spread through the household and the community. There is a higher case fatality rate of meningococcal disease in adults.

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**The impact on the Māori health areas of focus and Māori health outcomes**

Meningococcal infection rates are typically higher in Māori and Pacific people compared with the total population. In 2016, Māori had a disease rate of 2.6 per 100,000, 18 cases. Pacific people had the highest rate (4.28, 12 cases) and European or Other had the lowest rate (1.3, 39 cases).

**The impact on the health outcomes of population groups experiencing health disparities**

Meningococcal infection rates are typically higher in Pacific people compared to the total population. In 2016, Pacific people had the highest infection rate (4.28) of all ethnic groups.

Household crowding is an important risk factor for meningococcal disease, independent of ethnicity. In 2016 the highest age-specific disease rates were among those aged under 1 year (18.6 per 100,000, 11 cases) and 1–4 years (6.9 per 100,000, 17 cases).

## Health Benefit

**Details of the pharmaceutical under consideration**

Two meningococcal conjugate vaccines are currently listed on the Pharmaceutical Schedule and are under consideration for widening access.

- Meningoccocal C conjugate vaccine (currently NeisVac-C®)
- Meningoccocal ACWY conjugate vaccine (currently Menactra®)

NeisVac-C is indicated for immunisation of children from 8 weeks age, adolescents and adults. Children under 12 months require 2 doses given at last 2 months apart. A single dose is required for all others.

Menactra is indicated for immunisation of children from 9 months through to adults up to 55 years of age. For children aged 9 months to 23 months of age, 2 dose series at least 3 months apart is required. Note this vaccine was previously only used in children over 2 years of age. For older children and adults, a single dose is required.

**The health benefits to the person, family, whānau and wider society**

Both Neisvac-C and Menactra are effective against meningococcal disease serotype C. In addition, Menactra is also effective against serotypes A,Y,W.

Herd immunity is the best mechanism of control against meningococcal disease and universal vaccination with a conjugate vaccine for types A, C, W and Y aims to establish herd immunity.

In the UK, the funded schedule is primary dose at 3 months, 12-month booster and a further booster dose at 13-14 years. The programme has been successful in the UK, with cases of invasive group C disease being rare. Serotype C accounted for 4 cases out of 72 meningococcal cases in infants aged <1 year during 2016-17. (Public Health England 2017; Health Protection Report Volume 11 Number 38 – provided in Appendix 4). In 2016, the dose

at 3 months was removed when herd immunity was achieved, and the adolescent dose has been replaced by a conjugate quadrivalent vaccine (Ladhani et al. Arch Dis Child 2016:101:91-5 – provided in Appendix 4).

Herd immunity was seen as being key in the control of meningococcal disease in the UK. Prior to the introduction of MenC vaccination in adolescents and young adults, these age-groups accounted for 25% of carriage rates. A 71% reduction in MenC carriage was seen a year after the vaccine introduction. After just 2 months since the introduction of the MenACWY adolescent/fresher boosters, a small study has demonstrated a 39% decrease in MenY carriage and 36.2% decrease in combined CWY carriage in university students (Findlow H et al., Pediatric Drugs 2016;18(2):83-7).

Mass vaccination of adolescents and young adults with meningococcal C conjugate vaccine resulted in herd protection in unvaccinated age groups in the UK, the Netherlands and Italy (Balmer et al, Human Vaccines & Immunotherapeutics 2018: DOI 10.1080/21645515.2018.1454570 – provided in Appendix 4)).

Side effects are similar to other vaccines supplied in New Zealand, with pain at the injection site, myalgia and erythema being the most common.

## Suitability

**The features of the medicine or medical device that impact on use**

Menactra is registered with Medsafe and is currently supplied in New Zealand. There would be no change to current suitability resulting from any widening of access to these vaccines. Menactra is a quadrivalent vaccine, effective against MenACWY.

Menactra is indicated for active immunisation in people from 9 months to 55 years of age.

## Costs and Savings

**Costs and savings to pharmaceutical expenditure**

Costs and savings will be considered in a separate paper to PTAC which will be written following the close of the Immunisation RFP on 18 January 2019.

**Cost Effectiveness (combining the Health Benefits and Costs quadrants)**

Cost effectiveness will be considered in a separate paper to PTAC which will be written following the close of the Immunisation RFP on 18 January 2019.

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## APPENDICES

**Appendix 1:** February 2014 Immunisation Subcommittee minutes

**Appendix 2:** May 2018 Immunisation Subcommittee minutes

**Appendix 3:** September 2018 Immunisation Subcommittee minutes

**Appendix 4:** Public Health England 2017

Ladhani et al. 2015

Balmer et al. 2018

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## THE FACTORS FOR CONSIDERATION

Factors are presented here in the order they appear in the paper, without implying any ranking or relative importance.

### NEED

- The health need of the person
- The availability and suitability of existing medicines, medical devices and treatments
- The health need of family, whānau, and wider society
- The impact on the Māori health areas of focus and Māori health outcomes
- The impact on the health outcomes of population groups experiencing health disparities
- The impact on Government health priorities

### HEALTH BENEFITS

- The health benefit to the person
- The health benefit to family, whānau and wider society
- Consequences for the health system

### SUITABILITY

- The features of the medicine or medical device that impact on use by the person
- The features of the medicine or medical device that impact on use by family, whānau and wider society
- The features of the medicine or medical device that impact on use by the health workforce

### COSTS AND SAVINGS

- Health-related costs and savings to the person
- Health-related costs and savings to the family, whānau and wider society
- Costs and savings to pharmaceutical expenditure
- Costs and savings to the rest of the health system

**Minute of the February 2014 Immunisation Subcommittee relating to meningococcal C conjugate vaccine**

# 1 Meningococcal C conjugate vaccination

## Application

1.1 The Subcommittee considered a paper prepared by PHARMAC staff on widening access to meningococcal C vaccination eligibility, following the Committee's request for such a paper at its meeting of April 2013.

## Recommendation

1.2 The Subcommittee **deferred** making a recommendation on widening access to meningococcal C vaccinations, instead recommending that PHARMAC staff assess the effects of funding a meningococcal C vaccination programme for people in close living situations such as prisons, barracks, university halls of residence, and those boarding at boarding schools, as well as for universal vaccination of infants and adolescents or teenagers, particularly instituted with a catch-up programme.

1.3 The Subcommittee **recommended** that access to meningococcal C vaccine be amended to include vaccination of individuals with complement deficiency (acquired or inherited) with a high priority.

### Discussion

1.4 The Subcommittee noted that meningococcal C vaccinations had previously been discussed by the Subcommittee, and that Neisvac-C and Menactra will be listed from July 2014 for patients considered to be high-risk. Members noted that this paper discussed widening access to these vaccines to wider patient groups including universal vaccination. Some members expressed an interest in the combined HiB/Men C vaccination in order to reduce injection burden (i.e numbers of injections that would be given to a child) should universal vaccination against meningococcal C be introduced, but noted that this vaccine is not currently registered in New Zealand.

1.5 The Subcommittee noted New Zealand has a bimodal distribution of meningococcal disease incidence by age, with the highest age-specific disease incidence being in the very young (19.8 per 100,000 population aged less than one year and 5.6 per 100,000 in children aged 1 to 4 years) with a second peak of 4.8 per 100,000 population in the 15-19 year age group. The Subcommittee noted that of the 74 confirmed cases in 2012, 60% were serotyped as group B and 33% as group C.

1.6 The Subcommittee noted that mortality and morbidity associated with meningococcal C is higher than that associated with meningococcal B. The Subcommittee considered that current incidence of invasive meningococcal C disease in New Zealand are not as high as the rates other countries were experiencing prior to them implementing universal meningococcal C vaccination programmes.

1.7 The Subcommittee considered that meningococcal C conjugate vaccines would likely provide direct protection for around five years, possibly up to six to nine years, noting a study (Trotter & Maiden. Expert Rev Vaccines. 2009;8(7):851-61) where after ten years only 15% of vaccinated people maintained protection. Members noted that different kinds of conjugate vaccine would offer different durations of protection.

1.8 The Subcommittee considered that, for infants, the uptake rate of the vaccine would be as high as it is for other childhood vaccines, around 95%, if scheduled at the same time as other vaccines. Members considered that only around two-thirds coverage would be needed to provide herd immunity, which was considered to be a major component in any programme but was achieved via the use of a mass catch up programme for all children/adolescents at the start of instituting a universal programme. Members noted that the majority of benefit from mass vaccination resulted from reduced nasal carriage particularly in adolescents.

1.9 Members discussed when meningococcal C vaccines could be administered. Members noted that there is an existing scheduled immunisation at age 15 months, which could be suitable for the first dose of meningococcal C vaccine. Some members noted that, should the combined HiB/Men C vaccine become available, it could be given at age 12 months instead of 15 months. If universal varicella vaccine was also introduced this, could require an extra visit in the National Immunisation Schedule in the second year to avoid receiving too many injections at one visit. Members considered that one or two doses in adolescents could be appropriate, mentioning possible doses at age 11 years, the first year of high school (around 13 years), and 15 years.

1.10 The Subcommittee considered whether a catch-up programme would be needed, and noted that other countries such as the UK used catch up programmes when implementing their universal vaccination programmes to achieve herd immunity. The cost would depend on how a programme was implemented. Members discussed several options for a catch-up programme, including which ages would be eligible and whether it would be done through schools, as well as programmes used by the UK and Australia.

1.11 The Subcommittee noted the surveillance report prepared by ESR on the epidemiology of meningococcal disease in New Zealand, 2012, shows a higher incidence amongst Māori and Pacific peoples. Members noted there was no specific data of incidence of meningococcal C in patients with complement deficiency in New Zealand.

1.12 The Subcommittee noted a supplier's response to the vaccination RFP requesting consideration of funding quadravalent meningococcal C vaccination for patients with complement deficiency. Members noted that deficiencies in complement system protein may present with recurrent and severe bacterial infections, autoimmunity, or specific disorders resulting from inadequate regulation of complement activation. Members

noted that deficiency may be acquired or inherited and that the incidence and type of complement deficiency varies from country to country.

1.13 The Subcommittee noted that complement deficiency was not routinely screened for in New Zealand and that patient numbers were likely to be low. Members considered that patients would require frequent revaccination (every 5 years) to ensure protection.

1.14 The Subcommittee **recommended** that access to quadravalent meningococcal C vaccine be amended to include vaccination of individuals with complement deficiency (acquired or inherited) with high priority.

1.15 The Subcommittee considered that it needed more information before it could make a recommendation on widening access to meningococcal C vaccines to a universal vaccination programme. It recommended that PHARMAC examine meningococcal C vaccination programmes in other countries to help identify options, and then assess their potential cost-effectiveness to help identify optimal programmes; any analysis would ideally include widening access to various groups with various kinds of catch-up programmes, and vaccinating specific target groups such as people in prisons, barracks, student hostels, secondary boarding schools etc.

**Minute of the May 2018 Immunisation Subcommittee relating to meningococcal C vaccine**

# 1 Meningococcal C Vaccine

## Conflicts of Interests

1.1 Withheld under section 9(2)(ba)(i).

## Application

1.2 The Subcommittee reviewed analysis conducted by PHARMAC staff that modelled the costs of vaccination against meningococcal C (MenC) for two possible funding scenarios: people living in close living situations and universal childhood vaccination of infants, toddlers, and teenagers.

## Recommendation

1.3 The Subcommittee **deferred** making a recommendation regarding the funding of MenC vaccination for people living in close living situations and universal childhood vaccination of infants, toddlers, and teenagers, until more recent epidemiological data can be made available.

## Discussion

1.4 The Subcommittee noted that MenC vaccine eligibility was considered by the Immunisation Subcommittee in February 2014 (Immunisation Subcommittee Minutes, February 2014). At that time, a decision regarding widening access to MenC vaccines was deferred, and it was requested that PHARMAC staff assess the effect of funding MenC vaccines for people in close living situations as well as universal vaccination of infants and adolescents.

1.5 The Subcommittee noted that in New Zealand in 2016 there were 75 notified cases of meningococcal disease. Of the 67 strain-typed cases, 70% were serogroup B, 12% were serogroup C, 7% were serogroup W, and 10% were serogroup Y.

1.6 The Subcommittee noted that there was a recent outbreak of MenC in Fiji, with a mass vaccination program planned for Fijians aged 1-19 years. The Subcommittee also noted that the MenC rate has decreased in Australia and the UK following the introduction of vaccination programs, but the incidence of meningococcal W (MenW) disease is increasing.

1.7 The Subcommittee noted that there is a 10–20% serious disability rate for people who survive meningococcal disease, with those who experience significant complications requiring ongoing care and support.

1.8 The Subcommittee noted that mortality and morbidity were higher with MenC compared with meningococcal B (MenB) disease.

1.9 The Subcommittee noted that in New Zealand in 2016, the highest age-specific meningococcal rates were in infants aged under 1 year (18.6 per 100,000; 11 cases) and children aged 1–4 years (6.9 per 100,000; 17 cases).

1.10 The Subcommittee noted that by ethnicity, meningococcal disease rates tend to be highest in Pacific people followed by Māori. In New Zealand in 2016, meningococcal disease rates were 4.2 per 100,000 for Pacific people and 2.6 per 100,000 for Māori, compared with 1.6 per 100,000 for the total population.

1.11 The Subcommittee noted a systematic review and meta-analysis that investigated meningococcal carriage by age (Christensen et al. Lancet Infect Dis. 2010;10:853-61). The results identified carriage prevalence rates of 4.5% in infants, 23.7% in 19-year olds, and 7.8% in 50-year olds.

1.12 The Subcommittee noted that there are two meningococcal conjugate vaccines currently listed on the pharmaceutical schedule that are under consideration for widened access: a MenC conjugate vaccine (NeisVac-C) and a meningococcal ACYW-135 conjugate vaccine (Menactra).

1.13 The Subcommittee noted that both NeisVac-C and Menactra are funded for small sub-populations of patients who are considered to be high-risk; up to three doses and a booster every 5 years are funded for patients pre- and post-splenectomy and those with functional or anatomic asplenia, HIV, complement deficiency (acquired or inherited), or pre- or post-solid organ transplant; one dose for close contacts of meningococcal cases; and two doses for bone marrow transplant patients and for patients following immunosuppression (due to steroid or other immunosuppressive therapy must be for a period of greater than 28 days).

1.14 The Subcommittee noted that PHARMAC was currently reviewing vaccine criteria regarding immunosuppression to ensure criteria refer to pre-elective immunosuppression lasting longer than 28 days as well as following immunosuppression (Immunisation Subcommittee recommendation October 2016). The Subcommittee also noted that PHARMAC was reviewing the vaccine criteria to include patients who have been infected with meningococcal bacteria (Immunisation Subcommittee recommendation July 2017).

1.15 The Subcommittee noted the results of the MenC vaccination program carried out in the UK. It was noted that the initial program included doses at 3 months, 1 year, and a booster dose at 14 years. One year after the vaccine was introduced carriage rates dropped by 71% in adolescents and young adults. The Subcommittee noted that in 2015, the MenC vaccine was replaced with a MenACYW vaccine for the adolescent and first year university boosters due to the reported increase in MenW cases. Recent data indicate that since the introduction of the MenACYW vaccine, MenY carriage has decreased by 39%. The Subcommittee noted that once herd immunity was established, the 3-month dose was removed from the schedule in 2016. The Subcommittee considered that invasive MenC disease is now rare.

1.16 The Subcommittee considered that the evidence from the UK program suggests that a dose at 3 months of age would not be a necessary component of a universal MenC vaccination program. The Subcommittee considered that herd immunity would provide adequate protection provided there was good uptake.

1.17 The Subcommittee considered that neither NeisVac-C or Menactra would be associated with additional health benefit in an epidemic outbreak situation and for infants under 1 year of age who were at high risk (e.g., close contact of meningococcal case) as they are already funded.

1.18 The Subcommittee considered that Menactra (MenACYW) vaccine offered additional health benefit over NeisVac-C as it provides protection against four strains. The Subcommittee noted that for children aged 9–23 months, two doses of Menactra were required at least 3 months apart. The Subcommittee considered that if universal childhood vaccination was implemented, this would require a change to the current immunisation schedule to introduce an additional visit at 12 months of age. The Subcommittee considered that if other Schedule changes were also made, such as funding MenB, then a 12 month visit to deliver varicella, MenACYW and MenB would be suitable.

1.19 The Subcommittee considered that the patient population that would benefit most from MenC vaccination is adolescents. The Subcommittee considered that the evidence for health benefits from herd immunity with MenC vaccines was strong, and therefore universal immunisation would be optimal; however, it was noted that MenC is rare at this time.

1.20 The Subcommittee considered that the draft Health Needs Statement for meningococcal disease prepared by PHARMAC staff accurately described the health need associated with invasive meningococcal disease, apart from understating the morbidity associated with the disease. Members noted that some patients have multiple events such as amputation, deafness or loss of their nose.

1.21 The Subcommittee considered that PHARMAC staff estimates of the patient group size for people aged 13-19 living in close living situations was low. Members requested that PHARMAC staff provide updated group estimates for consideration at a future meeting. Members considered that the group size estimates for children aged <1 year and 1 to 4 years were acceptable.

1.22 The Subcommittee considered that MenC infection disproportionately affects Māori, Pacific people and other groups already experiencing health disparities relative to the wider New Zealand population.

1.23 The Subcommittee considered that MenC vaccine uptake was estimated to be: 20-30% for adolescents in close living situations, 90% for children aged 1-4 years and 90% for infants.

1.24 The Subcommittee considered that it agreed with the dosing schedules estimated by PHARMAC staff as follows for each group:

- 1 primary dose with a booster 5 years later for close living groups aged 13 to 19 years;
- 1 primary dose with a booster after 2 to 3 years for children aged 1 to 4 years;
- 2 doses in the first 12 months and a booster in the second year for infants aged <1 year.

1.25 The Subcommittee noted that adding an additional immunisation schedule visit would cost approximately an additional $1.2 million for vaccination claims, although the claim costs would be apportioned across all the vaccines delivered at that visit.

1.26 The Subcommittee considered that if a MenC vaccine was to be listed in the Pharmaceutical Schedule for universal infants immunisation, children aged 1 to 4 years and adolescents in close living situations, a quadrivalent meningococcal vaccine would be the most appropriate vaccine for New Zealand's epidemiology, however the Subcommittee deferred making a recommendation for the listing of meningococcal C vaccine. Members considered that they would like to see more epidemiological data for meningococcal disease to determine if it would be more effective to target access to close living situations or have universal immunisation with a dose for adolescents. The Subcommittee requested that PHARMAC staff provide recent epidemiological data to consider at the next meeting.

The Subcommittee considered that meningococcal C vaccine should not be listed in the Pharmaceutical Schedule for use during declared epidemics. Members considered that PHARMAC should assess such situations on a case by case basis.

**Minute of the September 2018 Immunisation Subcommittee relating to meningococcal C conjugate vaccine**

# 1. Meningococcal ACYW vaccine

### Conflicts of interests

1.1 The Chair noted that there were no conflicts of interest for this item.

### Application

1.2 The Subcommittee reviewed a paper from PHARMAC staff with updated epidemiological data regarding an application to fund meningococcal C vaccine and/or meningococcal ACYW vaccine for people in close living situations and universal childhood vaccination of infants, toddlers and teenagers.

### Recommendation

1.3 The Subcommittee **recommended** that a quadrivalent meningococcal ACYW vaccine be listed in the Pharmaceutical Schedule for toddlers in the second year of life (1 or 2 dose to be determined) and an adolescent dose and a catch up programme to be determined, with a high priority. The Subcommittee considered that it should review toddler dosing and possible options for a catch up programme following the commercial process due to be run later in 2018.

1.4 The Subcommittee **recommended** that meningococcal C vaccine for universal vaccination be declined.

### Discussion

1.5 The Subcommittee noted that at its May 2018 meeting it deferred making a recommendation regarding the funding of meningococcal C vaccination for people living in close living situations and universal childhood vaccination of infants, toddlers, and teenagers, until more recent epidemiological data can be made available. Members noted they had previously reviewed the evidence to support meningococcal vaccination.

1.6 The Subcommittee noted recent epidemiological data (up to August 2018) highlights that most cases of meningococcal disease in New Zealand are due to meningococcal B (MenB), but cases from groups other than B and C are increasing. Members noted that over the last five years, Meningococcal ACYW (MenACYW) vaccine would have covered twice as many isolates of *N. meningitidis* than the meningococcal C (MenC) vaccine. Members noted that the rate of group W and Y cases is increasing relative to group C.

1.7 The Subcommittee noted that the age most at risk of group B cases tends to be concentrated particularly in children under one year of age, but other meningococcal group cases tend to be spread more widely across the age groups. Members noted that the relatively short duration of protection from any meningococcal vaccination means that multiple doses could be required across a person's lifetime to maintain protection against vaccine strains.

1.8 The Subcommittee discussed a number of options for which immunisation visits would be optimal to deliver meningococcal vaccination if MenACYW or MenC was

funded. The Subcommittee considered that it would be preferable to give one or two doses in infancy/childhood and a further dose in adolescence. The Subcommittee considered that better herd immunity effects would be gained by starting vaccination with a MenACYW catch-up campaign followed by routine doses in the second year of life, followed by an adolescent dose. Members noted that adolescent vaccination reduces nasal carriage in the population with the highest carriage rates.

1.9 The Subcommittee noted that group W cases have increased in Australia to a greater extent than in New Zealand, although group W cases have increased in New Zealand in recent years. Members considered it was necessary to regularly monitor surveillance data for meningococcal cases.

1.10 The Subcommittee considered that the population size estimates by PHARMAC staff for people in close living situations, children aged 1-4 years and children under 1 year were reasonable. Members considered that the age distribution of cases favoured vaccination in the second year of life with a quadrivalent vaccine to also get coverage for other strains. Members considered that vaccination of adolescents or catch up campaigns could promote herd immunity, and more data on this was needed.

1.11 The Subcommittee considered that there was stronger evidence for including meningococcal vaccine in the Childhood Immunisation Schedule than for targeting adolescents in close living situations such as university halls of residence, boarding schools or military barracks. The Subcommittee considered that if a national MenC or MenACYW vaccination campaign was introduced, it should ideally include both infants and adolescents, rather than either group separately. The Subcommittee requested that they review the costings of possible meningococcal vaccination programmes, including adolescent catch up, following the commercial process for all vaccines that is scheduled to be released at the end of 2018. Members noted that logistically it would be easiest to deliver adolescent vaccination as part of the Year 11 and 12 Intermediate School programme, although waning efficacy of the vaccine delivered at this age would leave older adolescents less well protected.

1.12 The Subcommittee noted that the Immunisation Advisory Centre (IMAC) has recently completed a meningococcal antigen review. The Subcommittee requested that PHARMAC staff consider the antigen review and bring information back to the next Subcommittee meeting.

# NEW ZEALAND DATA SHEET

## 1 MENACTRA (SOLUTION FOR INJECTION)

Menactra® 0.5 mL solution for injection.

Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 mL dose of vaccine contains:

Active ingredients:

- Meningococcal polysaccharide* Group A 4.0 mcg/dose
- Meningococcal polysaccharide* Group C 4.0 mcg/dose
- Meningococcal polysaccharide* Group Y 4.0 mcg/dose
- Meningococcal polysaccharide* Group W-135 4.0 mcg/dose
- Diphtheria toxoid protein Approximately 48 mcg/dose

* Each of the four polysaccharides is conjugated to diphtheria toxoid.

Menactra is a sterile, clear to slightly turbid solution of *Neisseria meningitidis* purified capsular polysaccharides of groups A, C, Y and W-135, individually conjugated to a carrier protein. The protein is a purified *Corynebacterium diphtheriae* toxoid, *formalin-detoxified*. Each 0.5 mL dose of vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution. No preservative or adjuvant is added.

There is no latex in any component of the vial.

For the full list of excipients, see Section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection.

# 4 CLINICAL PARTICULARS

## 4.1 THERAPEUTIC INDICATIONS

Menactra is indicated for active immunisation in individuals from 9 months through 55 years of age for the prevention of invasive meningococcal disease caused by *N meningitidis* serogroups A, C, Y and W-135.

Menactra is not indicated for the prevention of meningitis caused by other microorganisms or for the prevention of invasive meningococcal disease caused by *N meningitidis* serogroup B.

Menactra is not indicated for treatment of meningococcal infections.

Menactra is not indicated for immunisation against diphtheria.

## 4.2 DOSE AND METHOD OF ADMINISTRATION

Menactra should be administered as a single 0.5 mL injection by the **intramuscular** route, preferably in the anterolateral thigh or deltoid region depending on the recipient's age and muscle mass.

### Primary Vaccination

- In children 9 through 23 months of age, Menactra is given as a 2-dose series 3 months apart.
- Individuals 2 through 55 years of age receive a single dose.

### Booster Vaccination

Menactra can also be used for booster vaccination in accordance with the national recommendation. For further information, refer to the current Immunisation Handbook.

Do not administer by intravascular injection.

Avoid injecting the vaccine intradermally or subcutaneously since clinical studies have not been conducted to establish safety and efficacy of the vaccine using these routes of administration.

For further information, refer to the current Immunisation Handbook.

Parenteral drug products should be inspected visually for container integrity, particulate matter and discoloration prior to administration, whenever solution and container permit.

Menactra must not be mixed with any vaccine in the same syringe. Therefore, separate injection sites and different syringes should be used in case of concomitant administration.

Product is for single use in one patient only. Discard any residue.

## 4.3 CONTRAINDICATIONS

Known hypersensitivity to any component of Menactra including diphtheria toxoid, or a life-threatening reaction after previous administration of a vaccine containing similar components, are contraindications to vaccine administration.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Do not administer by intravascular injection: ensure that the needle does not penetrate a blood vessel.

### Guillain-Barré Syndrome

Persons previously diagnosed with Guillain-Barré syndrome (GBS) may be at increased risk of GBS following receipt of Menactra. The decision to give Menactra should take into account the potential benefits and risks.

GBS has been reported in temporal relationship following administration of Menactra. The risk of GBS following Menactra vaccination was evaluated in a post-marketing retrospective cohort study (see Section 4.8).

### Prior to Vaccination

#### *Febrile or Acute Disease*

Vaccination must be postponed in case of acute severe febrile disease. However, a minor febrile or non-febrile illness (e.g., a cold) is not usually a reason to postpone immunisation.

#### *Anaphylaxis*

As with all injectable vaccines, appropriate medical treatment and supervision should be readily available for immediate use in case of a rare anaphylactic reaction following the administration of vaccine. As a precautionary measure, adrenaline (epinephrine) injection (1:1,000) must be immediately available in case of unexpected anaphylactic or serious allergic reactions.

#### *Individual History*

Before administration, all appropriate precautions should be taken to prevent adverse reactions. This includes a review of the patient's previous immunisation history, the presence of any contraindications to immunisation, the current health status, and history concerning possible sensitivity to the vaccine or similar vaccine.

Syncope has been reported following vaccination with Menactra. Procedures should be in place to prevent falling injury and manage syncopal reactions.

### Special Patient Groups

#### *Thrombocytopenia or Bleeding Disorders*

Menactra has not been evaluated in individuals with thrombocytopenia or bleeding disorders. As with any other vaccine administered intramuscularly, the vaccine risk versus benefit for individuals at risk of haemorrhage following intramuscular injection must be evaluated. If the decision is made to administer any product by intramuscular injection to such individuals, it should be given with caution, with steps taken to avoid the risk of haematoma formation following injection.

#### *Immunosuppression*

The immunogenicity of Menactra could be reduced by immunosuppressive treatment. In such cases it is recommended to postpone the vaccination until the end of the immunosuppression.

Menactra has been evaluated in about 300 Human Immunodeficiency Virus (HIV)-infected subjects. Menactra was safe and immunogenic in this population.

### Protection

Menactra may not protect 100% of individuals.

Menactra will only protect against *N meningitidis* A, C, Y and W-135 serogroups and will not protect against *N meningitidis* serogroup B disease or any other microorganisms.

Although an antibody response to diphtheria toxoid may occur, Menactra should not be considered as an immunising agent against diphtheria. No changes in the schedule for administering routine vaccines containing diphtheria toxoid are recommended.

### Use in the Elderly

Safety and effectiveness of Menactra in adults older than 55 years have not been established.

### Paediatric Use

Menactra is approved for use in children from 9 months of age.

### Effects on Laboratory Tests

Interference of Menactra with laboratory tests has not been studied.

## 4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

For information regarding concomitant administration of Menactra with other vaccines, see Sections 4.8 and 5.1.

If the vaccine is used in individuals under immunosuppressive therapy the expected immune response may not be obtained.

Menactra must not be mixed with any vaccine in the same syringe. Separate injection sites should be used in case of concomitant administration.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Pregnancy (Category B1)

In female mice intramuscularly injected with Menactra (at one fifth of the clinical dose per animal or at least 60 times the clinical dose on a mg/kg body weight basis) two weeks prior to mating and on gestation days 6 and 18, no maternal toxicity or effects on embryofetal and postnatal development were observed. However, no Sanofi Pasteur sponsored clinical trials with the primary objective of evaluating Menactra vaccine in pregnant women have been performed and spontaneously reported post-marketing data on the use of this vaccine in pregnant women are limited. The vaccine should be used during pregnancy only when clearly needed, such as during an outbreak or prior to necessary travel to an endemic area, and only following an assessment of the risks and benefits.

Sanofi Pasteur maintains a Menactra pregnancy registry to prospectively collect data from healthcare providers of patients who received Menactra during pregnancy. The objective of this pregnancy registry is to collect and analyse the outcome of exposure to Menactra during pregnancy and monitor for any potential safety signals that may arise in this population. To date, no safety concern for maternal or infant's health has been identified from this passive surveillance system. The experience with Menactra exposure during pregnancy, however, remains limited.

Healthcare providers are encouraged to inform sanofi pasteur of any pregnant women who receive Menactra for their inclusion in the vaccination pregnancy registry by calling 1800 818 806 (in Australia) or 0800 283 684 (in New Zealand).

### Breast-feeding

It is not known whether the active substances included in the vaccine are excreted in human milk, but antibodies to the polysaccharides have been found to be transferred to the suckling offspring of mice.

Animal studies conducted in mice have not shown any harmful effect on the postnatal development of offspring exposed through breastfeeding to Menactra-induced maternal antibodies. However, the effect on breast-fed infants of the administration of Menactra to their mothers has not been studied. The potential benefits to the mother and risks to the infant should be considered before administering Menactra to a nursing woman.

### Fertility

There were no effects on the mating performance or fertility of female mice intramuscularly injected with Menactra (at one fifth of the clinical dose) two weeks prior to mating. The effect of Menactra on male fertility has not been evaluated (see also Pregnancy).

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive or use machines have been performed.

## 4.8 UNDESIRABLE EFFECTS

### Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

#### *Children 9 Through 18 Months of Age*

The safety of Menactra was evaluated in 4 clinical studies that enrolled approximately 3,700 infants 9-18 months of age. At 12 months of age these children also received one or more other recommended vaccines [MMRV or MMR and Varicella Virus Vaccine Live (V), PCV7, Hepatitis A Vaccine (HepA)]. A control group of 997 children was enrolled at 12 months of age and received two or more childhood vaccines [MMRV (or MMR + V), PCV7, HepA] at 12 months of age (see Section 5.1).

The primary safety study was a controlled trial that enrolled 1256 children who received Menactra at 9 and 12 months of age. At 12 months of age these children received MMRV (or MMR + V), PCV7 and HepA.

#### *Individuals 2 Through 55 years of Age*

The safety of Menactra was evaluated in 8 clinical studies that enrolled 10,057 participants aged 2–55 years who received Menactra and 5266 participants who received Menomune–A/C/Y/W-135. The three primary safety studies were randomised, active-controlled trials that enrolled participants 2–10, 11–18 and 18–55 years of age, respectively.

#### *Solicited Adverse Events in the Primary Safety Studies*

The most frequently reported solicited injection site and systemic adverse reactions within 7 days following vaccination in children 9 months and 12 months of age (Table 1) were injection site tenderness and irritability.

The most frequently reported solicited local and systemic adverse reactions in children aged 2–10 years (Table 2) were injection site pain and irritability, respectively. Injection site redness, induration or swelling, diarrhoea, and drowsiness were also very common. In adolescents, ages 11-18 years (Table 3), and adults, ages 18-55 years (Table 4) the most commonly reported were injection site pain, headache and fatigue. Except for redness in adults, local reactions were more frequently reported after Menactra vaccination than after Menomune–A/C/Y/W-135 vaccination.

**Table 1 - Percentage of US Participants Reporting Solicited Adverse Reactions Within 7 Days Following Vaccine Administration at 9 Months and 12 Months of Age**

| | Menactra at 9 months of age N[d]=998 - 1002 | | | Menactra + PCV7[a]+ MMRV[b] + HepA[c] vaccines at 12 months of age N[d]=898 - 908 | | | PCV7[a]+ MMRV[b]+ HepA[c] vaccines at 12 months of age N[d]=302 - 307 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Reaction** | **Any** | **Grade 2** | **Grade 3** | **Any** | **Grade 2** | **Grade 3** | **Any** | **Grade 2** | **Grade 3** |
| **Local/Injection Site** | | | | | | | | | |
| **Tenderness[e]** | | | | | | | | | |
| Menactra Site | 37.4 | 4.3 | 0.6 | 48.5 | 7.5 | 1.3 | - | - | - |
| PCV7 Site | - | - | - | 45.6 | 9.4 | 1.6 | 45.7 | 8.3 | 0.3 |
| MMRV Site | - | - | - | 38.9 | 7.1 | 1.0 | 43.0 | 5.2 | 0.0 |
| HepA Site | - | - | - | 43.4 | 8.7 | 1.4 | 40.9 | 4.6 | 0.3 |
| **Erythema[f]** | | | | | | | | | |
| Menactra Site | 30.2 | 2.5 | 0.3 | 30.1 | 1.3 | 0.1 | - | - | - |
| PCV7 Site | - | - | - | 29.4 | 2.6 | 0.2 | 32.6 | 3.0 | 0.7 |
| MMRV Site | - | - | - | 22.5 | 0.9 | 0.3 | 33.2 | 5.9 | 0.0 |
| HepA Site | - | - | - | 25.1 | 1.1 | 0.0 | 26.6 | 0.7 | 0.0 |
| **Swelling[f]** | | | | | | | | | |
| Menactra Site | 16.8 | 0.9 | 0.2 | 16.2 | 0.9 | 0.1 | - | - | - |
| PCV7 Site | - | - | - | 19.5 | 1.3 | 0.4 | 16.6 | 1.3 | 0.7 |
| MMRV Site | - | - | - | 12.1 | 0.4 | 0.1 | 14.1 | 0.3 | 0.0 |
| HepA Site | - | - | - | 16.4 | 0.7 | 0.2 | 13.5 | 0.0 | 0.3 |
| **Systemic** | | | | | | | | | |
| Irritability[g] | 56.8 | 23.1 | 2.9 | 62.1 | 25.7 | 3.7 | 64.8 | 28.7 | 4.2 |
| Abnormal crying[h] | 33.3 | 8.3 | 2.0 | 40.0 | 11.5 | 2.4 | 39.4 | 10.1 | 0.7 |
| Drowsiness[i] | 30.2 | 3.5 | 0.7 | 39.8 | 5.3 | 1.1 | 39.1 | 5.2 | 0.7 |
| Appetite loss[j] | 30.2 | 7.1 | 1.2 | 35.7 | 7.6 | 2.6 | 31.9 | 6.5 | 0.7 |
| Vomiting[k] | 14.1 | 4.6 | 0.3 | 11.0 | 4.4 | 0.2 | 9.8 | 2.0 | 0.0 |
| Fever[l] | 12.2 | 4.5 | 1.1 | 24.5 | 11.9 | 2.2 | 21.8 | 7.3 | 2.6 |

[a] PCV7 (Prevnar®) = Pneumococcal 7-valent Conjugate Vaccine

[b] MMRV (ProQuad®) = Measles, Mumps, Rubella and Varicella Virus Vaccine Live

[c] HepA (VAQTA®) = Hepatitis A Vaccine, Inactivated

[d] N = The number of subjects with available data.

[e] Grade 2: cries and protests when injection site is touched, Grade 3: cries when injected limb is moved, or the movement of the injected limb is reduced.

[f] Grade 2: ≥1.0 inches to <2.0 inches, Grade 3: ≥2.0 inches.

[g] Grade 2: requires increased attention, Grade 3: inconsolable.

[h] Grade 2: 1 to 3 hours, Grade 3: >3 hours.

[i] Grade 2: not interested in surroundings or did not wake up for a feed/meal, Grade 3: sleeping most of the time or difficult to wake up.

[j] Grade 2: missed 1 or 2 feeds/meals completely, Grade 3: refuses ≥3 feeds/meals or refuses most feeds/meals.

[k] Grade 2: 2 to 5 episodes per 24 hours, Grade 3: ≥6 episodes per 24 hours or requiring parenteral hydration.

[l] Grade 2: >38.5°C to ≤39.5°C, Grade 3: >39.5°C.

**Table 2 - Percentage of US Participants 2–10 Years of Age Reporting Solicited Adverse Reactions Within 7 Days Following Vaccine Administration**

| | Menactra *N=1157 | | | Menomune–A/C/Y/W-135 *N=1027 | | |
|---|---|---|---|---|---|---|
| **Reaction** | **Any** | **Moderate** | **Severe** | **Any** | **Moderate** | **Severe** |
| Redness† | 21.8 | 4.6 | 3.9 | 7.9 | 0.5 | 0.0 |
| Swelling† | 17.4 | 3.9 | 1.9 | 2.8 | 0.3 | 0.0 |
| Induration† | 18.9 | 3.4 | 1.4 | 4.2 | 0.6 | 0.0 |
| Pain‡ | 45.0 | 4.9 | 0.3 | 26.1 | 2.5 | 0.0 |
| Drowsiness§ | 10.8 | 2.7 | 0.3 | 11.2 | 2.5 | 0.5 |
| Irritability‖ | 12.4 | 3.0 | 0.3 | 12.2 | 2.6 | 0.6 |
| Arthralgia¶ | 6.8 | 0.5 | 0.2 | 5.3 | 0.7 | 0.0 |
| Diarrhoea# | 11.1 | 2.1 | 0.2 | 11.8 | 2.5 | 0.3 |
| Anorexia** | 8.2 | 1.7 | 0.4 | 8.7 | 1.3 | 0.8 |
| Fever†† | 5.2 | 1.7 | 0.3 | 5.2 | 1.7 | 0.2 |
| Vomiting‡‡ | 3.0 | 0.7 | 0.3 | 2.7 | 0.7 | 0.6 |
| Rash§§ | 3.4 | | | 3.0 | | |
| Seizure§§ | 0.0 | | | 0.0 | | |

* N = The total number of subjects reporting at least one solicited reaction. The median age of participants was 6 years in both vaccine groups.

† Moderate: 1.0-2.0 inches, Severe: >2.0 inches.

‡ Moderate: interferes with normal activities, Severe: disabling, unwilling to move arm.

§ Moderate: interferes with normal activities, Severe: disabling, unwilling to engage in play or interact with others.

‖ Moderate: 1-3 hours duration, Severe: >3 hours duration.

¶ Moderate: Decreased range of motion due to pain or discomfort, Severe: unable to move major joints due to pain.

\# Moderate: 3-4 episodes, Severe: ≥ 5 episodes.

** Moderate: Skipped 2 meals, Severe: skipped ≥ 3 meals.

†† Oral equivalent temperature; Moderate: 38.4-39.4°C, Severe: ≥ 39.5°C.

‡‡ Moderate: 2 episodes, Severe: ≥3 episodes.

§§ These solicited adverse events were reported as present or absent only.

**Table 3 - Percentage of Participants 11–18 Years of Age Reporting Solicited Adverse Reactions Within 7 Days Following Vaccine Administration**

| | Menactra N*=2264 | | | Menomune–A/C/Y/W-135 N*=970 | | |
|---|---|---|---|---|---|---|
| **Reaction** | **Any** | **Moderate** | **Severe** | **Any** | **Moderate** | **Severe** |
| Redness‡ | 10.9† | 1.6† | 0.6† | 5.7 | 0.4 | 0.0 |
| Swelling‡ | 10.8† | 1.9† | 0.5† | 3.6 | 0.3 | 0.0 |
| Induration‡ | 15.7† | 2.5† | 0.3 | 5.2 | 0.5 | 0.0 |
| Pain§ | 59.2† | 12.8† | 0.3 | 28.7 | 2.6 | 0.0 |
| Headache‖ | 35.6† | 9.6† | 1.1 | 29.3 | 6.5 | 0.4 |
| Fatigue‖ | 30.0† | 7.5 | 1.1† | 25.1 | 6.2 | 0.2 |
| Malaise‖ | 21.9† | 5.8† | 1.1 | 16.8 | 3.4 | 0.4 |
| Arthralgia‖ | 17.4† | 3.6† | 0.4 | 10.2 | 2.1 | 0.1 |
| Diarrhoea¶ | 12.0 | 1.6 | 0.3 | 10.2 | 1.3 | 0.0 |
| Anorexia# | 10.7† | 2.0 | 0.3 | 7.7 | 1.1 | 0.2 |
| Chills‖ | 7.0† | 1.7† | 0.2 | 3.5 | 0.4 | 0.1 |
| Fever** | 5.1† | 0.6 | 0.0 | 3.0 | 0.3 | 0.1 |
| Vomiting†† | 1.9 | 0.4 | 0.3 | 1.4 | 0.5 | 0.3 |
| Rash‡‡ | 1.6 | | | 1.4 | | |
| Seizure‡‡ | 0.0 | | | 0.0 | | |

* N = The number of subjects with available data.
† Denotes $\rho < 0.05$ level of significance. The p values were calculated for each category and severity using Chi Square test.
‡ Moderate: 1.0-2.0 inches, Severe: >2.0 inches.
§ Moderate: Interferes with or limits usual arm movement, Severe: Disabling, unable to move arm.
‖ Moderate: Interferes with normal activities, Severe: Requiring bed rest.
¶ Moderate: 3-4 episodes, Severe: ≥ 5 episodes.
# Moderate: Skipped 2 meals, Severe: Skipped ≥ 3 meals.
** Oral equivalent temperature; Moderate: 38.5-39.4°C, Severe: ≥ 39.5°C.
†† Moderate: 2 episodes, Severe: ≥ 3 episodes.
‡‡ These solicited adverse events were reported as present or absent only.

**Table 4 - Percentage of Participants 18–55 Years of Age Reporting Solicited Adverse Reactions Within 7 Days Following Vaccine Administration**

| | Menactra N*=1371 | | | Menomune–A/C/Y/W-135 N*=1159 | | |
|---|---|---|---|---|---|---|
| **Reaction** | **Any** | **Moderate** | **Severe** | **Any** | **Moderate** | **Severe** |
| Redness‡ | 14.4 | 2.9 | 1.1† | 16.0 | 1.9 | 0.1 |
| Swelling‡ | 12.6† | 2.3† | 0.9† | 7.6 | 0.7 | 0.0 |
| Induration‡ | 17.1† | 3.4† | 0.7† | 11.0 | 1.0 | 0.0 |
| Pain§ | 53.9† | 11.3† | 0.2 | 48.1 | 3.3 | 0.1 |
| Headache‖ | 41.4 | 10.1 | 1.2 | 41.8 | 8.9 | 0.9 |
| Fatigue‖ | 34.7 | 8.3 | 0.9 | 32.3 | 6.6 | 0.4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Malaise‖ | 23.6 | 6.6† | 1.1 | 22.3 | 4.7 | 0.9 |
| Arthralgia‖ | 19.8† | 4.7† | 0.3 | 16.0 | 2.6 | 0.1 |
| Diarrhoea¶ | 16.0 | 2.6 | 0.4 | 14.0 | 2.9 | 0.3 |
| Anorexia# | 11.8 | 2.3 | 0.4 | 9.9 | 1.6 | 0.4 |
| Chills‖ | 9.7† | 2.1† | 0.6† | 5.6 | 1.0 | 0.0 |
| Fever** | 1.5† | 0.3 | 0.0 | 0.5 | 0.1 | 0.0 |
| Vomiting†† | 2.3 | 0.4 | 0.2 | 1.5 | 0.2 | 0.4 |
| Rash‡‡ | 1.4 | | | 0.8 | | |
| Seizure‡‡ | 0.0 | | | 0.0 | | |

* N = The number of subjects with available data.

† Denotes $\rho < 0.05$ level of significance. The *p* values were calculated for each category and severity using Chi Square test.

‡ Moderate: 1.0-2.0 inches, Severe: >2.0 inches.

§ Moderate: Interferes with or limits usual arm movement, Severe: Disabling, unable to move arm.

‖ Moderate: Interferes with normal activities, Severe: Requiring bed rest.

¶ Moderate: 3-4 episodes, Severe: ≥ 5 episodes.

# Moderate: Skipped 2 meals, Severe: Skipped ≥ 3 meals.

** Oral equivalent temperature; Moderate: 39.0-39.9°C, Severe: ≥40.0°C.

†† Moderate: 2 episodes, Severe: ≥ 3 episodes.

‡‡ These solicited adverse events were reported as present or absent only.

### *Booster Vaccination*

The safety of a booster dose of Menactra was evaluated in an open-label, multi-centre trial that enrolled 834 participants to receive a single dose of Menactra 4-6 years after a primary dose. The mean age of participants was 17.8 years (range: 15.0-53.7 years).

Booster vaccination with Menactra was generally safe and well tolerated among adolescents and young adults.

Overall rates of solicited injection-site reactions and solicited systemic reactions were similar to those observed in clinical trials that evaluated primary vaccination in adolescents and adults. The most common solicited injection-site and systemic reactions following booster vaccination were pain and myalgia.

### *Adverse Events in Concomitant Vaccine Studies*

#### *Local and Systemic Reactions when Given with Routine Paediatric Vaccines*

In the primary safety study, 1378 US children were enrolled to receive Menactra alone at 9 months of age and Menactra plus one or more other routinely administered vaccines (MMRV, PCV7 and HepA) at 12 months of age (N=961). Another group of children received two or more routinely administered vaccines (MMRV, PCV7 and HepA vaccines) (control group, n=321) at 12 months of age. The frequency of occurrence of solicited adverse events is presented in Table 1.

*Local and Systemic Reactions when Given with DTPa Vaccine*

In a clinical trial conducted in children 4 to 6 years of age, rates of local and systemic reactions were evaluated after administration of Menactra and DTpa. Menactra and DTPa had similar safety profiles and were well tolerated when administered concomitantly or separately.

*Local and Systemic Reactions when Given with dTpa Vaccine*

In a clinical trial conducted in adolescents 11 to 17 years of age, Tetanus Toxoid, reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (dTpa) and Menactra had similar safety profiles and were well tolerated when administered concomitantly or separately.

*Local and Systemic Reactions when Given with Td Vaccine*

The two vaccine groups reported similar frequencies of pain, induration, redness and swelling at the Menactra injection site, as well as, at the Td injection site. Pain was the most frequent local reaction reported at both the Menactra and Td injection sites.

The overall rate of systemic adverse events was higher when Menactra and Td vaccines were given concomitantly than when Menactra was administered 28 days after Td. In both groups, the most common reactions were headache and fatigue.

*Local and Systemic Reactions when Given with HPV Vaccine*

Concomitant administration of Menactra with HPV vaccines has been evaluated in two studies. In both studies, the safety profiles of the vaccines following concomitant administration were similar to those observed when the vaccines were given separately.

*Local and Systemic Reactions when Given with Typhim Vi Vaccine*

The two vaccine groups reported similar frequencies of pain, induration, redness and swelling at the Menactra injection site, as well as, at the Typhim Vi injection site. Pain was the most frequent local reaction reported at both the Menactra and Typhim Vi injection sites. More participants experienced pain after Typhim Vi vaccination than after Menactra vaccination (76% versus 47%). The majority (70%-77%) of local solicited reactions for both groups at either injection site were reported as mild and resolved within 3 days post-vaccination. In both groups, the most common systemic reaction was headache and fatigue.

**Adverse Reactions from Post-Marketing Surveillance**

Based on spontaneous reporting, the following additional adverse events have been reported during the commercial use of Menactra. These events have been very rarely reported, however as exact incidence rates cannot be calculated precisely, their frequency is qualified as “Not known”.

<u>Blood and lymphatic system disorders:</u>

Lymphadenopathy

Immune system disorders:

Hypersensitivity reactions such as anaphylaxis/anaphylactic reaction, wheezing, difficulty breathing, upper airway swelling, urticaria, erythema, pruritus, hypotension

Nervous system disorders:

Guillain-Barré syndrome, paraesthesia, vasovagal syncope, dizziness, convulsion, facial palsy, acute disseminated encephalomyelitis, transverse myelitis

Musculoskeletal and connective tissue disorders:

Myalgia

General disorders and administrative site conditions:

Large injection site reactions, including extensive limb swelling have been reported. These reactions may be associated with erythema, warmth, tenderness or pain at the injection site.

**Post-marketing Safety Study**

The risk of GBS following receipt of Menactra was evaluated in a US retrospective cohort study using healthcare claims data from 9,578,688 individuals 11 through 18 years of age, of whom 1,431,906 (15%) received Menactra. Of 72 medical chart-confirmed GBS cases, none had received Menactra within 42 days prior to symptom onset. An additional 129 potential cases of GBS could not be confirmed or excluded due to absent or insufficient medical chart information. In an analysis that took into account the missing data, estimates of the attributable risk of GBS ranged from 0 to 5 additional cases of GBS per 1,000,000 vaccinees within the 6 week period following vaccination.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia) or https://nzphvc.otago.ac.nz/reporting/ (New Zealand).

## 4.9 OVERDOSE

No case of overdose has been reported.

For general advice on overdose management, contact the Poisons Information Centre, telephone number 13 11 26 (Australia) or the National Poisons Centre, 0800 POISON or 0800 764 766 (New Zealand).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: meningococcal vaccine, ATC code: J07AH08

### Mechanism of action

The presence of bactericidal anti-capsular meningococcal antibodies has been associated with protection from invasive meningococcal disease. Menactra induces the production of bactericidal antibodies specific to the capsular polysaccharides of serogroups A, C, Y and W-135.

### Clinical Trials

#### *Immunogenicity*

The immunogenicity of Menactra has been studied in three clinical trials in infants 9 through 18 months of age, in four clinical trials among children 2 through 10 years of age, and in six clinical trials among adolescents and adults 11 through 55 years of age.

Menactra induces the production of antibodies specific to the capsular polysaccharides of all vaccine serogroups (A, C, Y and W-135), which are capable of killing the corresponding bacteria. Immunogenicity was assessed by measuring these functional antibodies in a serum bactericidal assay (SBA) using baby rabbit (SBA-BR) or human (SBA-HC) serum as the complement source.

The response to vaccination following one or two doses of vaccine administered to children 9 through 18 months of age and following one dose of vaccine administered to children 2 through 10 years of age was evaluated by the proportion of subjects having an SBA-HC antibody titre of 1:8 or greater, for each serogroup. In adolescents and adults, the response to vaccination was evaluated by the proportion of subjects with a 4-fold or greater increase in bactericidal antibody to each serogroup as measured by SBA-BR.

Immunogenicity of Menactra has been studied in three clinical trials in approximately 2250 infants 9 through 18 months of age where one or two doses were administered either alone or with concomitant paediatric vaccine(s) (Measles, Mumps, Rubella and Varicella Virus vaccine Live [MMRV] or Pneumococcal 7-valent Conjugate (Diphtheria CRM197 Protein) vaccine [PCV7). A subset of the participants in these trials received Menactra concomitantly with MMRV + *Haemophilus Influenza* type b vaccine [Hib].

Immunogenicity was evaluated in three comparative, randomised, US, multi-centre, active controlled clinical trials that enrolled children (2–10 years old), adolescents (11–18 years old), and adults (18–55 years old). Participants received a dose of Menactra (N=2526) or Menomune–A/C/Y/W-135 (N=2317). For all age groups studied, sera were obtained before and approximately 28 days after vaccination.

In each of the trials, there were no substantive differences in demographic characteristics between the vaccine groups, between immunogenicity subsets or the overall study population.

### *Immunogenicity in Children 9 through 23 Months of Age*

In a primary study (MTA44), the majority of the participants in groups that received the second dose of Menactra alone or with concomitant paediatric vaccines achieved SBA-HC titres ≥1:8 for all serogroups. Groups that received the second dose of Menactra alone had ≥ 91% of subjects achieving an SBA-HC titre ≥1:8 for serogroups A, C, and Y, and ≥86% for serogroup W 135 (Table 5). When the second dose of Menactra was given concomitantly with MMRV (or MMRV+Hib) or with PCV7, the percentages of subjects with SBA-HC titres ≥1:8 were high (>90% for serogroups A, C and Y, and >81% for serogroup W 135). SBA HC GMTs were high for all serogroups.

**Table 5 - Proportions of Subjects With SBA HC Antibody Titres ≥ 1:8 and SBA-HC Geometric Mean Titres After the 12 Month Menactra Vaccination, by Study (Per-Protocol Population)**

| | | Group 1 Menactra at 9 months and 12 months (M[a] =272–277) [1] | Group 2 Menactra at 9 months and Menactra + MMRV at 12 months (M[a]=177–180) [1] | Group 3 Menactra at 9 months and Menactra + PCV7 at 12 months (M[a]=264–267) [1] |
|---|---|---|---|---|
| | | % or GMT | % or GMT | % or GMT |
| % of subjects with titre ≥1:8 | A | 95.6 | 92.7 | 90.5 |
| | C | 100.0 | 98.9 | 97.8 |
| | Y | 96.4 | 96.6 | 95.1 |
| | W-135 | 86.4 | 88.2 | 81.2 |
| GMT | A | 54.9 | 52.0 | 41.0 |
| | C | 141.8 | 161.9 | 109.5 |
| | Y | 52.4 | 60.2 | 39.9 |
| | W-135 | 24.3 | 27.9 | 17.9 |

[a] [1] M: number of subjects in the per-protocol population with valid test results. M varies as indicated depending on the evaluation criterion being considered. Percentages are based on M.

Administration of Menactra to toddlers at 12 months and 15 months of age (N=65) was evaluated in a US study. Prior to the first dose, 33.3% of participants had an SBA-HC titre ≥1:8 to Serogroup A, and 0-2% to serogroups C, Y and W-135. After the second dose, percentages of participants with an SBA-HC titre ≥1:8 were: 85.2%, serogroup A; 100.0%, serogroup C; 96.3%, serogroup Y; 96.2%, serogroup W-135.

In the same study, a group of infants received Menactra at 9 months and 15 months of age (N=65). Prior to the first dose 43.9% of participants had an SBA-HC titre ≥1:8 to serogroup A, and 0-2.2% to serogroups C, Y and W135. After the second dose, percentages of participants with an SBA-HC titre ≥1:8 were: 89.4%, serogroup A; 100.0%, serogroup C; 94.0%, serogroup Y; 92.0%, serogroup W-135.

In MTA26, a Phase II, dose schedule-optimisation study, after a first dose of Menactra given at 9 or 12 months of age in Groups 1, 2 and 3, the percentage of subjects achieving SBA-HC titres ≥ 8 ranged from 51.9% to 75.8% for serogroup A, from 82.9% to 85.4% for serogroup C, from 20.6% to 34.6% for serogroup Y, and from 17.6% to 26.7% for serogroup W-135.

After the second dose of Menactra given at 12 or 15 months, the percentage of subjects in each group achieving titres ≥ 8 ranged from 85.2% (for serogroup A) to 100% (for serogroup C) (Table 6).

**Table 6 - Percentage of Subjects with SBA-HC Antibody Titres ≥ 8 (Per-Protocol Population)**

| Serogroup | Timeframe | Group 1 Menactra at 9 months and 12 months % (95% CI[a]) | Group 2 Menactra at 9 months and 15 months % (95% CI[a]) | Group 3 Menactra at 12 months and 15 months % (95% CI[a]) |
|---|---|---|---|---|
| A | Post Dose 1 | 75.8 (57.7, 88.9) | 66.7 (51.0, 80.0) | 51.9 (37.6, 66.0) |
| | Post Dose 2 | 88.9 (73.9, 96.9) | 89.4 (76.9, 96.5) | 85.2 (72.9, 93.4) |
| C | Post Dose 1 | 82.9 (66.4, 93.4) | 85.4 (72.2, 93.9) | 84.6 (71.9, 93.1) |
| | Post Dose 2 | 100.0 (90.5, 100.0) | 100.0 (92.9, 100.0) | 100.0 (93.4, 100.0) |
| Y | Post Dose 1 | 20.6 (8.7, 37.9) | 24.4 (12.9, 39.5) | 34.6 (22.0, 49.1) |
| | Post Dose 2 | 94.6 (81.8, 99.3) | 94.0 (83.5, 98.7) | 96.3 (87.3, 99.5) |
| W-135 | Post Dose 1 | 23.5 (10.7, 41.2) | 26.7 (14.6, 41.9) | 17.6 (8.4, 30.9) |
| | Post Dose 2 | 91.7 (77.5, 98.2) | 92.0 (80.8, 97.8) | 96.2 (86.8, 99.5) |

[a] The 95% CI was calculated using the Exact method

This study also evaluated a single dose of Menactra at 15 months or 18 months of age. After a single dose of Menactra at 15 or 18 months, responses for serogroups A and C were similar to those in Groups 1, 2 and 3 after the first dose of Menactra. Responses after the single dose of Menactra at 15 or 18 months for serogroups Y and W-135 were higher than those after a single dose of Menactra at 9 months. However, overall the results confirmed that 2 doses of Menactra are preferred to elicit a high immune response for all 4 serogroups in subjects aged 9 through 15 months.

### *Immunogenicity in Children 2 through 10 Years of Age*

Of 1408 enrolled children 2-10 years old, immune responses evaluated in a subset of Menactra participants (2–3 years old, n=52; 4–10 years old, n=84) and Menomune–A/C/Y/W-135 participants (2–3 years old, n=53; 4–10 years old, n=84) were comparable for all four serogroups (Table 7 and Table 8).

**Table 7 - Comparison of Bactericidal Antibody Responses* to Menactra and Menomune–A/C/Y/W-135 28 Days After Vaccination for a Subset of Participants Aged 2–3 Years**

| | | Menactra N‡=48-52 | | Menomune–A/C/Y/W-135 N‡=50-53 | |
|---|---|---|---|---|---|
| **Serogroup** | | | (95% CI)§ | | (95% CI)§ |
| A | % ≥ 1:8† | 73 | (59, 84) | 64 | (50, 77) |
| | GMT | 10 | (8, 13) | 10 | (7, 12) |
| C | % ≥ 1:8† | 63 | (48, 76) | 38 | (25, 53) |
| | GMT | 27 | (14, 52) | 11 | (5, 21) |
| Y | % ≥ 1:8† | 88 | (75, 95) | 73 | (59, 84) |
| | GMT | 51 | (31, 84) | 18 | (11, 27) |
| W-135 | % ≥ 1:8† | 63 | (47, 76) | 33 | (20, 47) |
| | GMT | 15 | (9, 25) | 5 | (3, 6) |

* Serum Bactericidal Assay with an exogenous human complement (SBA-H) source.

† The proportion of participants achieving at least an SBA-H titre of 1:8 was assessed using a 10% non-inferiority margin and a one-sided Type I error rate of 0.025.

‡ N = Number of subset participants with at least one valid serology result at Day 0 and Day 28.

§ The 95% CI for the Geometric Mean Titre (GMT) was calculated based on an approximation to the normal distribution.

**Table 8 - Comparison of Bactericidal Antibody Responses* to Menactra and Menomune–A/C/Y/W-135 28 Days After Vaccination for a subset of Participants Aged 4–10 Years**

| | | Menactra N‡=84 | | Menomune–A/C/Y/W-135 N‡=84 | |
|---|---|---|---|---|---|
| **Serogroup** | | | (95% CI)§ | | (95% CI)§ |
| **A** | % ≥ 1:8† | 81 | (71, 89) | 55 | (44, 66) |
| | GMT | 19 | (14, 26) | 7 | (6, 9) |
| **C** | % ≥ 1:8† | 79 | (68, 87) | 48 | (37, 59) |
| | GMT | 28 | (19, 41) | 12 | (7, 18) |
| **Y** | % ≥ 1:8† | 99 | (94, 100) | 92 | (84, 97) |
| | GMT | 99 | (75, 132) | 46 | (33, 66) |
| **W-135** | % ≥ 1:8† | 85 | (75, 92) | 79 | (68, 87) |
| | GMT | 24 | (18, 33) | 20 | (14, 27) |

* Serum Bactericidal Assay with an exogenous human complement (SBA-H) source.

† The proportion of participants achieving at least an SBA-H titre of 1:8 was assessed using a 10% non-inferiority margin and a one-sided Type I error rate of 0.025.

‡ N = Number of subset participants with at least one valid serology result at Day 0 and Day 28.

§ The 95% CI for the Geometric Mean Titre (GMT) was calculated based on an approximation to the normal distribution.

In the subset of participants 2-3 years of age with undetectable pre-vaccination titres (i.e., < 4 at Day 0), seroconversion rates (defined as ≥ 8 at Day 28) were similar between the Menactra and Menomune–A/C/Y/W-135 recipients. Menactra participants achieved seroconversion

rates of: 57%, serogroup A (n=12/21); 62%, serogroup C (n=29/47); 84%, serogroup Y (n=26/31); 53%, serogroup W-135 (n=20/38). The seroconversion rates for Menomune–A/C/Y/W-135 recipients were 55%, serogroup A (n=16/29); 30%, serogroup C (n=13/43); 57%, serogroup Y (n=17/30); 26%, serogroup W-135 (n=11/43).

In the subset of participants 4-10 years of age, percentages of participants that achieved seroconversion were similar between the Menactra and Menomune–A/C/Y/W-135 recipients. Menactra participants achieved seroconversion rates of: 69%, serogroup A (n=11/16); 81%, serogroup C (n=50/62); 98%, serogroup Y (n=45/46); 69%, serogroup W-135 (n=27/39). The seroconversion rates for Menomune–A/C/Y/W-135 recipients were 48%, serogroup A (n=10/21); 38%, serogroup C (n=19/50); 84%, serogroup Y (n=38/45); 68%, serogroup W-135 (n=26/38).

### *Immunogenicity in Adolescents 11 through 18 years of Age*

Results from the comparative clinical trial conducted in 881 adolescents aged 11-18 years showed that the immune responses to Menactra and Menomune–A/C/Y/W-135 were similar for all four serogroups (Table 9).

**Table 9 - Comparison of Bactericidal Antibody Responses* to Menactra and Menomune–A/C/Y/W-135 28 Days after Vaccination for Participants Aged 11–18 Years**

| | | Menactra N‡=423 | | Menomune–A/C/Y/W-135 N‡=423 | |
|---|---|---|---|---|---|
| **Serogroup** | | | (95% CI)§ | | (95% CI)§ |
| **A** | % ≥ 4-fold rise† | 92.7 | (89.8, 95.0) | 92.4 | (89.5, 94.8) |
| | GMT | 5483 | (4920, 6111) | 3246 | (2910, 3620) |
| **C** | % ≥ 4-fold rise† | 91.7 | (88.7, 94.2) | 88.7 | (85.2, 91.5) |
| | GMT | 1924 | (1662, 2228) | 1639 | (1406, 1911) |
| **Y** | % ≥ 4-fold rise† | 81.8 | (77.8, 85.4) | 80.1 | (76.0, 83.8) |
| | GMT | 1322 | (1162, 1505) | 1228 | (1088, 1386) |
| **W-135** | % ≥ 4-fold rise† | 96.7 | (94.5, 98.2) | 95.3 | (92.8, 97.1) |
| | GMT | 1407 | (1232, 1607) | 1545 | (1384, 1725) |

* Serum Bactericidal Assay with baby rabbit complement (SBA-BR).

† Menactra was non-inferior to Menomune–A/C/Y/W-135. Non-inferiority was assessed by the proportion of participants with a 4-fold or greater rise in SBA-BR titre for *N meningitidis* serogroups A, C, Y and W-135 using a 10% non-inferiority margin and a one-sided Type I error rate of 0.05.

‡ N = Number of participants with valid serology results at Day 0 and Day 28.

§ The 95% CI for the Geometric Mean Titre (GMT) was calculated based on an approximation to the normal distribution.

In participants with undetectable pre-vaccination titres (i.e., less than 8 at Day 0), seroconversion rates (defined as a ≥ 4-fold rise in Day 28 SBA titres) were similar between the Menactra and Menomune–A/C/Y/W-135 recipients. Menactra participants achieved seroconversion rates of: 100%, serogroup A (n=81/81); 99%, serogroup C (n=153/155); 98%, serogroup Y (n=60/61); 99%, serogroup W-135 (n=161/164). The seroconversion rates for

Menomune–A/C/Y/W-135 recipients were 100%, serogroup A (n=93/93); 99%, serogroup C (n=151/152); 100%, serogroup Y (n=47/47); 99%, serogroup W-135 (n=138/139).

### *Immunogenicity in Adolescents and Adults following Booster Vaccination*

In an open-label, multi-centre trial conducted in the US (MTA77), 834 participants < 56 years of age were enrolled to receive a single dose of Menactra 4-6 years after a primary dose at ≥ 11 years of age. The mean age of subjects was 17.8 years. The rapidity and magnitude of the anti-meningococcal antibody increases following booster vaccination with Menactra suggested these were anamnestic responses.

Among the randomly chosen subset of trial participants for whom immune responses at Day 6 were assessed (n=112), 86.6%, 91.1%, 94.6%, and 92.0% achieved ≥4-fold rises in SBA-H antibody titres for Serogroups A, C, Y, and W-135, respectively. The proportions of participants (n=781) who achieved ≥4-fold rises in SBA-H antibody titres by Day 28 were 95.0%, 95.3%, 97.1%, and 96% for Serogroups A, C, Y, and W-135, respectively. The proportions of participants who achieved an SBA-H titre ≥1:8 by Day 28 were >99% for each serogroup.

### *Immunogenicity in Adults 18 through 55 years of Age*

Results from the comparative clinical trial conducted in 2554 adults aged 18-55 years showed that the immune responses to Menactra and Menomune–A/C/Y/W-135 were similar for all four serogroups (Table 10).

**Table 10 - Comparison of Bactericidal Antibody Responses* to Menactra and Menomune–A/C/Y/W-135 28 Days After Vaccination for Participants Aged 18–55 Years**

| | | Menactra N‡=1280 | | Menomune–A/C/Y/W-135 N‡=1098 | |
|---|---|---|---|---|---|
| **Serogroup** | | | (95% CI)§ | | (95% CI)§ |
| A | % ≥ 4-fold rise† | 80.5 | (78.2, 82.6) | 84.6 | (82.3, 86.7) |
| | GMT | 3897 | (3647, 4164) | 4114 | (3832, 4417) |
| C | % ≥ 4-fold rise† | 88.5 | (86.6, 90.2) | 89.7 | (87.8, 91.4) |
| | GMT | 3231 | (2955, 3533) | 3469 | (3148, 3823) |
| Y | % ≥ 4-fold rise† | 73.5 | (71.0, 75.9) | 79.4 | (76.9, 81.8) |
| | GMT | 1750 | (1597, 1918) | 2449 | (2237, 2680) |
| W-135 | % ≥ 4-fold rise† | 89.4 | (87.6, 91.0) | 94.4 | (92.8, 95.6) |
| | GMT | 1271 | (1172, 1378) | 1871 | (1723, 2032) |

* Serum Bactericidal Assay with baby rabbit complement (SBA-BR).

† Menactra was non-inferior to Menomune–A/C/Y/W-135. Non-inferiority was assessed by the proportion of participants with a 4-fold or greater rise in SBA-BR titre for *N meningitidis* serogroups A, C, Y and W-135 using a 10% non-inferiority margin and a one-sided Type I error rate of 0.05.

‡ N = Number of participants with valid serology results at Day 0 and Day 28.

§ The 95% CI for the GMT was calculated based on an approximation to the normal distribution.

In participants with undetectable pre-vaccination titres (i.e., less than 8 at Day 0), seroconversion rates (defined as a ≥ 4-fold rise in Day 28 SBA titres) were similar between the Menactra and Menomune–A/C/Y/W-135 recipients. Menactra participants achieved seroconversion rates of: 100%, serogroup A (n=156/156); 99%, serogroup C (n=343/345); 91%, serogroup Y (n=253/279); 97%, serogroup W-135 (n=360/373). The seroconversion rates for Menomune–A/C/Y/W-135 recipients were 99%, serogroup A (n=143/144); 98%, serogroup C (n=297/304); 97%, serogroup Y (n=221/228); 99%, serogroup W-135 (n=325/328).

***Concomitant Vaccine Administration***

*PCV7, MMR, V, MMRV, HepA, Hib*

In clinical trials conducted in children younger than 2 years of age, Pneumococcal 7-valent Conjugate Vaccine (PCV7), Measles, Mumps, and Rubella Virus Vaccine (MMR), Varicella Virus Vaccine Live (V), Measles, Mumps, Rubella and Varicella Virus Vaccine Live (MMRV), Hepatitis A Vaccine (HepA) or Haemophilus influenzae type b Vaccine (Hib) were co-administered with the second dose of Menactra at 12 months of age. Menactra and all these vaccines had similar safety profiles when administered concomitantly or separately at 12 months of age. The immunogenicity profiles of Menactra and MMRV, MMR+V, or Hib were also similar when these vaccines were given concomitantly or separately.

When Menactra was administered concomitantly with PCV, antibody responses to 3 of the 7 serotypes in PCV (MTA37) and to serogroup W-135 (MTA44) of Menactra did not meet the non-inferiority criteria. Given the high antibody response rates to all PCV serotypes when assessed by either ELISA or OPA, and considering that >81% of subjects achieved SBA-HC antibody titres ≥1:8 for all 4 serogroups of Menactra, it is unlikely that there will be any impact on the clinical efficacy of either of these vaccines when administered concomitantly.

*Diphtheria, Tetanus and Acellular Pertussis*

The concomitant use of Menactra and Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTPa) was evaluated in a double-blind, randomised clinical trial (MTA43) conducted in 881 participants aged 4-6 years.

When Menactra as administered 30 days after DTPa (and Inactivated Polio Vaccine (IPV)) [Group 1], significantly lower SBA-HC GMTs to all 4 meningococcal serogroups were observed compared to Menactra (and IPV) administered 30 days prior to DTPa [Group 3]. When Menactra was administered concomitantly with DTPa [Group 2], SBA-HC GMTs to meningococcal serogroups A, C, and W-135 were non-inferior to those observed after Menactra (and IPV) [Group 3]. The non-inferiority criterion was marginally missed for meningococcal serogroup Y. Non-inferiority of SBA-HC GMTs following concomitant administration of Menactra and DTPa compared to those after concomitant Menactra and IPV was concluded if the upper limit of the 2-sided 95% CI of (GMTGroupC divided by GMTGroupB) computed separately for each of the serogroup was < 2.

**Table 11 - Bacterial Antibody Responses* 30 days Following Menactra Administered Alone or Concomitantly with DTPa or IPV**

| | | Vaccines administered at Visit 1 and 30 days later at Visit 2 | | | | | |
|---|---|---|---|---|---|---|---|
| | | Group 1 | | Group 2 | | Group 3 | |
| | Visit 1 | DTPa +IPV | | Menactra +DTPa | | Menactra + IPV | |
| | Visit 2 | Menactra | | IPV | | DTPa | |
| | | N‡=250 | | N‡=238 | | N‡=121 | |
| Serogroup | | | (95% CI)§ | | (95% CI)§ | | (95% CI)§ |
| A | % ≥ 1:8† | 49.6 | (41.0; 58.3) | 67.2 | (58.4; 75.1) | 64.4 | (54.4; 73.6) |
| | GMT | 6.7 | (5.7; 8.0) | 10.8 | (8.7; 13.3) | 10.4 | (8.1; 13.3) |
| C | % ≥ 1:8† | 20.3 | (13.9; 28.0) | 50.4 | (41.5; 59.2) | 50.5 | (40.5; 60.5) |
| | GMT | 3.3 | (2.7; 3.9) | 8.1 | (6.3; 10.5) | 7.8 | (5.8; 10.7) |
| Y | % ≥ 1:8† | 44.2 | (35.8; 52.9) | 80.2 | (72.3; 86.6) | 88.5 | (80.7; 93.9) |
| | GMT | 6.5 | (5.1; 8.2) | 18.1 | (14.2; 22.9) | 26.2 | (20.0; 34.4) |
| W-135 | % ≥ 1:8† | 55.1 | (46.4; 63.5) | 87.8 | (80.9; 92.9) | 82.7 | (74.0; 89.4) |
| | GMT | 8.4 | (6.7; 10.6) | 22.8 | ( 18.5; 28.1) | 21.7 | (16.6; 28.4) |

* Serum Bactericidal Assay with an exogenous human complement (SBA-HC) source.

† The proportion of participants achieving an SBA-HC titre of at least 1:8, 30 days after Menactra.

‡ N = Total number of the subjects in the study population per group.

§ 95% CI for the proportions are calculated based on the Clopper-Pearson Exact method and normal approximation for that of the GMTs.

Significantly lower antibody responses to all 4 meningococcal serogroups were observed when Menactra was administered 1 month after DTPa. As a measure of precaution, in cases where Menactra and DTPa vaccine are to be administered at 4 through 6 years of age, preference should be given to simultaneous administration of the 2 vaccines or administration of Menactra prior to DTPa vaccine.

*Tetanus, reduced Diphtheria and Acellular Pertussis*

The concomitant use of Menactra and Tetanus Toxoid, reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (dTpa) and Menactra was evaluated in a clinical trial conducted in adolescents 11 to 17 years of age. The concomitant administration of dTpa and Menactra induced antibody responses to all 4 meningococcal serogroups A, C, Y, and W-135 that were non-inferior to those observed when Menactra was administered separately.

*Tetanus and Diphtheria*

The concomitant use of Menactra and Tetanus and Diphtheria Toxoids Adsorbed, For Adult Use (Td, manufactured by Sanofi Pasteur Inc.) was evaluated in a double-blind, randomised, controlled clinical trial conducted in 1021 participants aged 11–17 years. For meningococcal serogroups C, Y and W-135, the proportion of participants with a 4-fold or greater rise in SBA titre was higher when Menactra was given concomitantly with Td than when Menactra was given one month following Td. The clinical relevance of this finding has not been fully

evaluated. No interference was observed in the immune response to the tetanus and diphtheria components following concomitant vaccination.

*Human Papillomavirus*

Concomitant administration of Menactra with HPV vaccines has been evaluated in two studies. In one study, Menactra was co-administered with human papillomavirus bivalent (Types 16 and 18) AS04-adjuvanted vaccine (HPV2) alone and with Tdap to females 11 – 18 years of age. In another study, Menactra was co-administered with both human papillomavirus quadrivalent (Types 6, 11, 16 and 18) vaccine (HPV4) and dTpa to females and males 10 – 17 years of age. Concomitant administration of Menactra and dTpa with HPV did not interfere with the immune responses to any antigens in these vaccines.

*Typhoid Vi Polysaccharide Vaccine, Typhim Vi®*

The concomitant use of Menactra and Typhim Vi (recommended for certain travellers) was evaluated in a double-blind, randomised, controlled clinical trial conducted in 945 participants aged 18–55 years. The immune response to Menactra and to Typhim Vi when given concurrently was comparable to the immune response when Menactra or Typhim Vi was given alone.

### 5.2 PHARMACOKINETIC PROPERTIES

No pharmacokinetic studies have been performed.

### 5.3 PRECLINICAL SAFETY DATA

**Genotoxicity**

No genotoxicity studies have been conducted with Menactra.

**Carcinogenicity**

No carcinogenicity studies have been conducted with Menactra.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

- Sodium chloride 4.35 mg
  (within 0.85% Physiological Saline[†] and 0.5M Phosphate Buffered Saline[§], pH 6.8)
- Dibasic sodium phosphate 0.348 mg
  (within 0.5M Phosphate Buffered Saline[§], pH 6.8)
- Monobasic sodium phosphate 0.352 mg
  (within 0.5M Phosphate Buffered Saline[§], pH 6.8)

[†] 0.85% Physiological Saline is composed of sodium chloride in Water for Injections.

§ 0.5M Phosphate Buffered Saline is composed of sodium chloride, dibasic sodium phosphate and monobasic sodium phosphate in Water for Injections.

### 6.2 INCOMPATIBILITIES

Menactra must not be mixed with any vaccine in the same syringe.

### 6.3 SHELF LIFE

24 months.

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze). Product that has been exposed to freezing should not be used. Do not use after expiration date.

Protect from light.

### 6.5 NATURE AND CONTENTS OF CONTAINER

Vial, 1 Dose

Packs of 1 vial (marketed) or 5 vials (not marketed)

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements.

## 7 MEDICINE SCHEDULE

Prescription

## 8 SPONSOR

Australia:

**sanofi-aventis australia pty ltd**
Talavera Corporate Centre - Building D
12-24 Talavera Road
Macquarie Park NSW 2113
Australia

Tel: 1800 818 806

New Zealand:

**sanofi-aventis new zealand pty ltd**
Level 8,
56 Cawley St
Ellerslie
Auckland
New Zealand

Tel: 0800 283 684

## 9 DATE OF FIRST APPROVAL

08 March 2012

## 10 DATE OF REVISION OF THE TEXT

05 July 2018

### SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|---|---|
| **All** | Reformat of Data sheet including addition of text to align with requirements. |
| **4.2** | Addition of booster vaccination in accordance with the national recommendation. |
| **4.3** | Removal of febrile or acute disease contraindications. |
| **4.4** | Update to protection and febrile or acute disease precautions. |
| **4.6** | Update to use in pregnancy. |
| **4.8** | Addition of safety data following booster and co-administration with other vaccines. Addition of new safety data from post-marketing surveillance. |
| **5.1** | Addition of immunogenicity data in children 9-23 months of age, immunogenicity in adolescents/adults following booster and co-administration with other vaccines. |

PHARMAC
Pharmaceutical Management Agency

# PTAC MEMORANDUM

**From:** Therapeutic Group Manager

**Date:** February 2019

## Costs and Savings: Meningococcal ACWY vaccination eligibility

## QUESTIONS TO PTAC

*Note to PTAC members: These questions have been identified by PHARMAC staff as being particularly relevant to the application. Please feel free to provide additional information as appropriate.*

### Need

1. Does meningococcal disease disproportionally affect:
    - Māori?
    - Pacific people?
    - Other groups already experiencing health disparities relative to the wider New Zealand population (eg. NZ Dep 9-10 deprivation, refugees/asylum seekers)?
2. What is the strength and quality of evidence in relation to health needs due to meningococcal disease?

### Health benefit

3. Does meningococcal ACWY vaccine provide any additional health benefit or create any additional risks compared with other funded treatment options? If so, what benefits or risks are different from alternative treatments?
4. Which patient population would benefit most from meningococcal ACWY vaccine?
5. What is the strength and quality of evidence, including its relevance to NZ, for health benefits that may be gained from meningococcal ACWY vaccine?
6. Would meningococcal ACWY vaccine produce a health benefit for family, whānau or wider society, additional to the health benefits for people at risk of meningococcal disease? If so how, and what is the strength and quality of evidence for this benefit?
7. Should meningococcal ACWY criteria be widened, are there any consequences to the health system that have not been noted in the application?

### Suitability

8. Are there any non-clinical features of the meningococcal ACWY vaccine formulation that may impact on use, either by the patient, by family, or by healthcare workers, that have not been considered in the application?

## Costs and savings

9. What health care resource utilisation implications are associated with key meningococcal ACWY sequelae, including physical, neurological, psychological and behavioural?

## Recommendations

10. Should meningococcal ACWY vaccine be listed in the Pharmaceutical Schedule for adolescents in close living situations?

    10.1. If listing is recommended, does the Committee recommend a catch-up programme? If so, how long should the catch-up period be?

    10.2. If listing is recommended, how does the Committee define the eligible group, and which vaccine is recommended?

    10.3. If listing for adolescents in close living situations is recommended, what priority rating would you give to this proposal? **[low / medium / high / only if cost-neutral]**?

11. Should meningococcal ACWY vaccine be listed in the Pharmaceutical Schedule for a universal adolescent dose?

    11.1. If listing is recommended, does the Committee recommend a catch-up programme? If so, how long should the catch-up period be?

    11.2. If listing for a universal adolescent dose is recommended, what priority rating would you give to this proposal? **[low / medium / high / only if cost-neutral]**?

12. Should meningococcal ACWY vaccine be listed in the Pharmaceutical Schedule for children aged 1 to 4 years?

    12.1. If listing is recommended, does the Subcommittee recommend a catch-up programme?

    12.2. If listing for children aged 1 to 4 years is recommended, what priority rating would you give to this proposal? **[low / medium / high / only if cost-neutral]**?

13. Does the Committee have any recommendations additional to the application?

## PURPOSE OF THIS PAPER

The purpose of this paper is to provide costs and savings and cost effectiveness information to the Committee regarding the funding of meningococcal ACWY (Men ACWY) quadrivalent vaccine for people in close living situations and universal childhood vaccination of infants, toddlers and teenagers. The Committee is considering a paper on meningococcal ACWY quadrivalent vaccine at this meeting, in which all the Factors for Consideration were addressed apart from Costs and Savings. This section has been completed following the close of the vaccines RFP.

## DISCUSSION

### Costs and Savings

**Health-related costs and savings to the person, their family, whānau and wider society**

Meningococcal C vaccines are currently funded for high risk patients only. The vaccines are available for private purchase for those patients not eligible for funded vaccination.

Delivery of vaccine typically requires GP consultation, vaccination purchase and administration (e.g. a nurse). Should any sub-populations or all the relevant populations be provided access through the National Immunisation Schedule (NIS), they would incur no vaccination dose or administration costs if their administration coincides with the existing visits in the NIS.

Cost per vaccination varies in private practices, with prices per dose of $70 to $110 for NeisVac-C and $90 to $165 for Menactra reported. PHARMAC data summarising the distribution of the Menactra vaccination in the last 5 years is provided in the table below, indicating a small, but not insignificant (and growing) population.

**Table 1 Estimated Private Menactra Uptake 2015 to 2018 (Financial Year)**

| Financial Year | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|
| Menactra Patients | 1,004 | 1,566 | 1,782 | 2,112 |

**Costs and savings to pharmaceutical expenditure**

Analysis here focuses on the populations requested by the Immunisation Subcommittee in September 2018. The Subcommittee recommended with a high priority that a quadrivalent meningococcal ACWY vaccine be listed in the Pharmaceutical Schedule for:

1. Toddlers in the second year (i.e. 12 to 23 months) of life (1 or 2 doses, to be determined);
2. An adolescent dose (i.e., for those entering the ages 13 to 19 cohort), including an initial catch-up programme (to be determined);

3. Adolescents living in closed-living populations (school dormitories, university and technology institute on-site living quarters and prison populations).

*Estimated Patient Populations*

Closed-Living Populations

The following population data was presented to the Immunisation Sub-committee in August 2018 and deemed reflective of the patient populations previously requested to be considered by the Subcommittee. Data from the New Zealand Ministry of Education website "Education Counts" (www.educationcounts.gov.nz) estimates 174,000 students enrolled at Universities during 2016; enrolments have fluctuated in the last decade but overall remain at the same level as 2008. Considering technology institutes and other tertiary providers there was an estimated 416,000 tertiary students (FTE) in New Zealand in 2016. Of these, it is estimated based on publicly available information these providers have 16,000 residential students in close living quarters, although this number could be higher.

Further, there are approximately 294,000 students enrolled in schools as at 1 July 2017 between the ages of 13 and 19 (only 1,765 aged 19). According to Education Counts, as of August 2018, there are 96 boarding schools in New Zealand, with an estimated aggregate boarding school population of 13,440. For reference, Education Counts estimated approximately 10,000 boarding school students in 2002.

Focusing on the specified closed-living sub-populations requested by the Immunisation Subcommittee in May 2018, it is assumed there are approximately 8,700 'new entrants' into the defined sub-populations annually and approximately 46,000 in total in these sub-populations (with 37,500 therefore deemed 'catch up' in any given year).

The table below summarises these estimates. It is assumed that the prison population continues to grow and thus new entrants to the system are incremental; for the armed forces, it is assumed new entrants are aged 18 to 19 and replace older members; these ages and the concept of 'replacement' is also assumed for new entrants in the university and boarding school populations.

**Table 2 Estimated Relevant Sub-Populations**

| Patient Sub-population | Total (new) | Total (catchup) |
|---|---|---|
| Prisoners (sentenced) | 74 | 7,409 |
| Armed forces (barracks/quarters) | 921 | 8,287 |
| Tertiary education residential students (dormitories, residential living blocks) | 5,000 | 11,000 |
| Boarding school students (dormitories) | 2,700 | 10,800 |
| **Total** | **8,695** | **37,496** |

Sources: New Zealand Defence Force (/www.nzdf.mil.nz/downloads/pdf/public-docs/2017/2016-2017-nzdf-annual-report.pdf); New Zealand Department of Corrections (Department of Corrections New Zealand, 2017 (http://www.corrections.govt.nz/resources/research_and_statistics/quarterly_prison_statistics.html); Education Counts (NZ Ministry of Health, www.educationcounts.govt.nz/statistics/tertiary-education/participation, www.educationcounts.govt.nz/statistics/schooling/student-numbers/6028, www.educationcounts.govt.nz/find-school).

Notes: Estimated boarding/close-living populations sourced from going to websites of the individual education providers listed in data tables provided by 'Education Counts'. Some listed boarding schools at 'Education Counts' did not specify boarding student population numbers; imputed values have been used based on average numbers of boarding schools with specified boarding populations (approximately 65% of the 96 listed schools had boarding student numbers published). Tertiary education residential student numbers are based on publicly available information referencing listed tertiary education providers from 'Education Counts' but may be higher.

Toddlers and Adolescents

**Table 3** summarises the estimated 'overall' New Zealand population for toddlers and adolescents, based on the Immunisation Subcommittee's acknowledgement of key incidence peaks in the 0 to 4 and 13 to 19 age populations. For reference, the estimated overall New Zealand population between the ages of 0 and 19 is approximately 1.25 million; each age within this range typically has approximately 60,000 population. Note that for adolescents there will be some minimal overlap with the close-living sub-populations identified above.

**Table 3 Estimated overall New Zealand population: infants and adolescents/teenagers**

| **Population Definition and Age Bracket** | **Population** |
|---|---|
| Toddlers: 1 to 2 years (second year of life) | 60,000 |
| Adolescents: 13 to 19 years | 435,000 |
| **Total** | **495,000** |

Source: Stats NZ, August 2018 (http://archive.stats.govt.nz/infoshare/ViewTable.aspx?pxID=1f01ca00-da2d-4805-a7ea-96a0388966e2 )

**Cost per patient**

The relevant vaccine is Menactra® (groups A, C, Y, and W135). Cost per patient reflects total number of doses and the price per dose assumed following PHARMAC's RFP process of Withheld.

***Please note that all vaccine price information is confidential and not to be shared outside the Subcommittee. ***

*Cost for defined adolescent sub-populations (i.e., aged 13 to 19) and those living in high-risk closed living sub-populations*

Patients in both the adolescent and the closed-living sub-populations are assumed to require only one dose. There are several possible cohort dosing approaches, so for Committee briefing purposes, both yearly 'entrants' into these sub-populations and 'catch-up' programs (whereby everyone in the sub-population in the first year is eligible), then followed in subsequent years by vaccination of 'entrants' only to these sub-population cohorts are presented. There is a cost of Withheld per patient. The base case assumes an administration cost per dose of approximately $20, resulting in a total per patient regimen cost of Withheld.

*Cost for toddlers (1 to 2 years)*

For children aged 1 to 2 years, either a 1 or 2 dose regimen (taken within 12 months) is possible. For the purposes of this analysis, 2 doses are assumed (total per patient regimen cost of Withheld). The base case assumes no administration cost.

**Estimated Incremental Total Cost of Listing**

Combined Pharmaceutical Budget (CPB) and District Health Board (DHB) cost impact associated with listing over the first five years has been estimated for the populations as defined above. All five-year budget impacts have been calculated at net present value (NPV), discounted at 8% per annum.

It should be noted that vaccination is expected to reduce the number of patients experiencing acute and long-term consequences of infection and thus associated health care resource utilisation. Initial analysis by PHARMAC staff indicates that although this an important outcome of any vaccination program, that relative to vaccination program costs, this is anticipated to be relatively small in comparison. Should PHARMAC proceed with listing, PHARMAC staff will undertake more detailed analysis of health care resource cost impacts. We seek PTAC comment on health care resource utilisation associated with key meningococcal sequelae, including physical, neurological, psychological and behavioural (amputation, blindness, hearing (including deafness), anxiety, facial scarring, severe neurological impairment etc.).

For the purposes of analysis by PHARMAC staff, uptake reflects feedback from the Immunisation Sub-committee in May 2018 on the specified sub-populations:

- 20% to 30% in closed living situations for adolescents (i.e. aged 13 to 19 in university residence, prisons and boarding schools); and
- 90% for children aged 1-2 years and adolescents aged 13 to 19 years. NIS full coverage targets for infants/children are typically 95%, but data from Ministry of Health as at March 2018 shows this has not quite been achieved (12-month completion is estimated at 93.6%, 24-months at 92%). A 90% uptake rate for adolescents assumes vaccination occurring in schools.

**Table 4** summarises the estimated yearly CPB and DHB budget impacts of vaccinating 'entrants' only into defined closed living sub-populations. Over five years the estimated NPV DHB impact would be approximately Withheld ( Withheld CPB). Administration costs are assumed.

**Table 4 Estimated yearly CPB and DHB impacts of immunising 'entrants' into closed populations only**

| Item | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Patients (25% uptake) | 2,174 | 2,174 | 2,174 | 2,174 | 2,174 |
| **Vaccination Costs** | | | | | |
| First dose | Withheld | Withheld | Withheld | Withheld | Withheld |
| Second dose | | | | | |
| Booster | | | | | |
| **Total CPB impact** | Withheld | Withheld | Withheld | Withheld | Withheld |
| **Administration Costs** | | | | | |
| First/Second/Booster dose | $44,589 | $44,589 | $44,589 | $44,589 | $44,589 |
| **Total DHB impact** | Withheld | Withheld | Withheld | Withheld | Withheld |

Notes: Individual year amounts undiscounted. Uptake reflects midpoint of likely uptake provided by Immunisation Sub-committee in May 2018 for closed living situations. Analysis assumes Menactra vaccine cost of approximately Withhe per dose. Administration cost of approximately $20 per dose assumed.

**Table 5** summarises the estimated yearly CPB and DHB budget impacts of vaccinating 'entrants' and catch-up in defined closed living sub-populations. Over five years the estimated NPV DHB impact would be approximately Withhel ( Withheld under ). All patients in the closed living sub-populations including catch-ups would be vaccinated in year one, with vaccinations in subsequent years reflecting new entrants only. Administration costs are assumed.

**Table 5 Estimated yearly CPB and DHB impacts of immunising entrants and catch-up population into closed sub-populations**

| Item | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Patients (25% uptake) | 11,548 | 2,174 | 2,174 | 2,174 | 2,174 |
| **Vaccination Costs** | | | | | |
| First dose | Withheld | Withheld | Withheld | Withheld | Withheld |
| Second dose | | | | | |
| Booster | | | | | |
| **Total CPB impact** | Withheld | Withheld | Withheld | Withheld | Withheld |
| **Administration Costs** | | | | | |
| First/Second/Booster dose | $236,849 | $44,589 | $44,589 | $44,589 | $44,589 |
| **Total DHB impact** | Withheld | Withheld | Withheld | Withheld | Withheld |

Notes: Individual year amounts undiscounted. Uptake reflects midpoint of likely uptake provided by Immunisation Sub-committee in May 2018 for closed living situations. Analysis assumes Menactra vaccine cost of approximately Withhe per dose. Administration cost of approximately $20 per dose assumed.

**Table 6** summarises the estimated yearly CPB and DHB budget impacts of vaccinating 'entrants' into adolescent populations only. This is considering patients in this age bracket regardless of their living situation (closed sub-populations was previously separately considered, see **Table 4** and **Table 5**). Note as such the marginal overlap in projected budget impact as a result. Over five years the estimated NPV DHB impact would be approximately Withheld ( Withheld under ). Administration costs are assumed.

**Table 6 Estimated yearly CPB and DHB impacts of immunising 'entrants' into adolescent population only**

| Item | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Patients (90% uptake) | 56,700 | 56,700 | 56,700 | 56,700 | 56,700 |
| **Vaccination Costs** | | | | | |
| First dose | Withheld | Withheld | Withheld | Withheld | Withheld |
| Second dose | | | | | |
| Booster | | | | | |
| **Total CPB impact** | Withheld | Withheld | Withheld | Withheld | Withheld |
| **Administration Costs** | | | | | |
| First/Booster dose | $1,162,917 | $1,162,917 | $1,162,917 | $1,162,917 | $1,162,917 |
| **Total DHB impact** | Withheld | Withheld | Withheld | Withheld | Withheld |

Notes: Individual year amounts undiscounted. Uptake assumes vaccination undertaken in school setting. Analysis assumes Menactra cost of approximately Withhe per dose. Administration cost of $20 per dose assumed.

**Table 7** summarises the estimated five-year CPB and DHB impact of vaccinating entrants and providing patient cohort 'catch-up in the first year for ages 13 to 19. This is considering patients in this age bracket regardless of their living situation (closed sub-populations was previously considered see **Table 4** and **Table 5**). Note as such the marginal overlap in projected budget impact as a result. Over five years the estimated NPV DHB impact would be approximately Withheld ( Withheld under ). Administration costs are assumed.

**Table 7 Estimated yearly CPB and DHB impacts of immunising adolescents ages 13 to 19: including catch up**

| Item | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Patients (90% uptake) | 390,600 | 56,700 | 56,700 | 56,700 | 56,700 |
| **Vaccination Costs** | | | | | |
| First dose | Withheld | Withheld | Withheld | Withheld | Withheld |
| Second dose | | | | | |
| Booster | | | | | |
| **Total CPB impact** | Withheld | Withheld | Withheld | Withheld | Withheld |
| **Administration Costs** | | | | | |
| First/Booster dose | $8,011,206 | $1,162,917 | $1,162,917 | $1,162,917 | $1,162,917 |
| **Total DHB impact** | Withheld | Withheld | Withheld | Withheld | Withheld |

Notes: Individual year amounts undiscounted. Uptake assumes vaccination undertaken in school setting. Analysis assumes Menactra cost of approximately Withhe per dose. Administration cost of $20 per dose assumed.

**Table 8** summarises the estimated yearly CPB and DHB impacts of immunising toddlers only (between the ages of 1 to 2). Over five years the estimated NPV DHB impact would be approximately Withheld ( Withheld under ). No administration costs are assumed.

**Table 8 Estimated CPB and DHB impact of toddlers (1 to 2 years)**

| Item | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Patients (90% uptake) | 54,000 | 54,000 | 54,000 | 54,000 | 54,000 |
| **Vaccination Costs** | | | | | |
| First dose | Withheld | Withheld | Withheld | Withheld | Withheld |
| Second dose | Withheld | Withheld | Withheld | Withheld | Withheld |
| Booster (2nd year) | | | | | |
| **Total CPB impact** | Withheld | Withheld | Withheld | Withheld | Withheld |
| **Administration Costs** | | | | | |
| First/Second/Booster dose | | | | | |
| **Total DHB impact** | Withheld | Withheld | Withheld | Withheld | Withheld |

Notes: Individual year amounts undiscounted. Uptake reflects likely uptake estimated provided to Immunisation Sub-committee in May 2018 for toddlers. Analysis assumes Menactra cost of approximately Withhe per dose. No administration costs are assumed based on scheduling being in line with the New Zealand National Immunisation Schedule.

**Table 9** summarises the yearly DHB (vaccine dose plus administration) budget impacts for each scenario described above.

**Table 9 Summary of total DHB budget impact for each funding scenario**

| Population groups | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | 5-year NPV |
|---|---|---|---|---|---|---|
| Entrants only, closed populations | Withheld | Withheld | Withheld | Withheld | Withheld | Withhel |
| Entrants and catch-up, closed | Withheld | Withheld | Withheld | Withheld | Withheld | Withhe |
| Entrants only, adolescent populations | Withheld | Withheld | Withheld | Withheld | Withheld | Withhel |
| Entrants and catch-up, adolescent | Withheld | Withheld | Withheld | Withheld | Withheld | Withhel |
| Toddlers, 1 to 2 years | Withheld | Withheld | Withheld | Withheld | Withheld | Withhel |

Notes: Individual year amounts undiscounted.

### Cost Effectiveness (combining the Health Benefits and Costs quadrants)

PHARMAC staff have not undertaken formal cost-effectiveness analysis specifically of the introduction of the Menactra ACWY vaccine. Withheld under section 9(2)(b)(ii) and 9(2)(ba)(i)

Withheld under section 9(2)(b)(ii) and 9(2)(ba)(i)

Withheld under section 9(2)(b)(ii) and 9(2)(ba)(i)

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Withheld under section 9(2)(b)(ii) and 9(2)(ba)(i)

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Withheld under section 9(2)(b)(ii) and 9(2)(ba)(i)

Withheld under section 9(2)(b)(ii) and 9(2)(ba)(i)

Withheld under section 9(2)(b)(ii) and 9(2)(ba)(i)

Withheld under section 9(2)(b)(ii) and 9(2)(ba)(i)

This model therefore does not readily adhere to the guidance of PHARMAC's *Prescription for Pharmacoeconomic Analysis (PFPA) Methods for Cost-Utility Analysis* (i.e., "Models should avoid unnecessary complexity and should be transparent, well described and reproducible").

Due to being unable to adapt the model specifically to assess Menactra, PHARMAC staff make indicative reference to analysis undertaken as part of the funding of vaccine for the November 2018 Northland meningococcal W outbreak is provided for reference, noting that it does not

consider coverage of C or Y strains. This analysis considered three potential patient populations for vaccination.

1. Children aged 9 months – 4 years and adolescents aged 14 – 19 years (one Menactra dose).
2. All children aged 9 months – 4 years and adolescents aged 14 – 19 years, but with patients 12 months to 2 years having Nimenrix.
3. All children aged 9 months to people aged under 20 years old. One dose to all people aged under 20 years. Menactra for children aged 9 months to 12 months, and 4 years to 19 years. Nimenrix for children aged 12 months to 2 years.

In undertaking the analysis, the growing incidence and severity of the W strain (as reflected in the case fatality ratio (CFR)) was acknowledged, along with the potential for a higher proportion of cases experiencing long term sequelae. It was acknowledged that the assessment focused specifically on a high outbreak geographical region. Revising the assumption about the input price (to Withheld), indicative cost-effectiveness results have been estimated for PTAC consideration of the above defined groups:

1. Children aged 9 months – 4 years and adolescents aged 14 – 19 years – Withheld under Withheld under section QALYs per $1m respectively.
2. All children aged 9 months – 4 years and adolescents aged 14 – 19 years – Withheld under section 9(2)(b)(ii), 9(2)(ba) QALYs per $1m respectively.
3. All children aged 9 months to people aged under 20 years old. Menactra for children aged 9 months to 12 months, and 4 years to 19 years – Withheld under section QALYs per $1m for all sub-populations.

## Attachments

1. Appendix 1 – February 2014 Immunisation Subcommittee minutes
2. Appendix 2 – May 2018 Immunisation Subcommittee minutes