Medicines Adverse Reactions Committee

Meeting date	**3 July 2018**	Agenda item	3.2.1
Title	**Bexsero (recombinant Meningococcal group B vaccine) RMP**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Medicine Bexsero	**Active constituent** Recombinant *Neisseria meningitidis* group B NHBA fusion protein 50 µg Recombinant *Neisseria meningitidis* group B NadA protein 50 µg Recombinant *Neisseria meningitidis* group B fHbp fusion protein 50 µg Outer membrane vesicles (OMV) from *Neisseria meningitidis* group B strain NZ 98/254 measured as amount of total protein containing the PorA P1.42, 25 µg		**Sponsor** GlaxoSmithKline
Funding	To be considered by PTAC for inclusion in the 2019 National Immunisation Programme.		
Previous MARC meetings	This vaccine has not been discussed previously. Meningococcal B vaccine and chronic fatigue was discussed at the 13 September 2007 meeting.		
International action	Approved in Australia (August 2013), Europe (January 2013), USA (January 2015), Canada (December 2013) and other countries worldwide. The vaccine was introduced to the UK schedule in September 2015.		
Prescriber Update	None for this vaccine. Surveillance of adverse events following MeNZB Immunisation November 2004 (www.medsafe.govt.nz/profs/PUArticles/MeNZB.htm).		
Schedule	Prescription medicine except when administered by an approved pharmacist to a person 16 years of age or over.		
Usage data	[redacted]		
Advice sought	**The Committee is asked to advise on the following:** – Are any changes required to the RMP? – Are there any elements that require clarification or further information from the company? – Are there any actions required should this vaccine be funded (eg, additional monitoring and/or reporting, information for consumers and/or healthcare professionals etc.)?		

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1.0 PURPOSE

Medsafe has received a new medicine application from GlaxoSmithKline (GSK) for Bexsero (meningococcal B vaccine). Priority assessment under the abbreviated process is currently being conducted by Medsafe. A decision on approval by Medsafe is required by end of October 2018 for it to be reviewed by PHARMAC's Pharmacology and Therapeutics Advisory Committee (PTAC) meeting in November 2018 as part of the 2019 National Immunisation Schedule (NIS) review.

Due to previous interest with another meningococcal B vaccine product (MeNZB) when it was used during 2004 to 2008, Medsafe considered it appropriate to request a Risk Management Plan (RMP) for Bexsero from the company. The purpose of this paper is to seek the Committee's advice on whether any additional post-market activities are required in New Zealand should Bexsero be approved.

2.0 BACKGROUND

2.1 Meningococcal disease [1]

Meningococcal disease is a bacterial infection that causes two very serious illnesses: meningitis and septicaemia.

Strains

Meningococcal disease is caused by the bacterium *Neisseria meningitidis.* There are several different groups of meningococcal bacteria including groups A, B, C, Y and W135. These groups of bacteria can be further divided into specific strains.

- Most cases in New Zealand are caused by group B.
- The next most common is group C.
- There have previously been limited outbreaks of meningococcal disease due to group A.
- Cases of meningococcal disease caused by groups W135 and Y are rare in New Zealand.

Spread

Meningococcal bacteria are difficult to catch because they don't live for very long outside of the body. They pass from one person to another through secretions from the nose or throat, during close or prolonged contact, for example:

- by coughing or sneezing (by droplet spread)
- by kissing
- by sharing eating or drinking utensils, toothbrushes, pacifiers.

Those at risk

Anyone can potentially get meningococcal disease but it is more common in:

- babies and young children
- teenagers and young adults
- people with a weak immune system – for example those having chemotherapy treatment or have HIV
- close contacts of meningococcal disease cases (eg, same household)
- those having other respiratory infections (eg, flu)
- people living in shared accommodation such as halls of residence (university), boarding school and hostels
- those living in overcrowded housing
- those exposed to tobacco smoke.

Meningococcal disease can cause death or permanent disability, such as deafness.

NZ epidemiology (2016) [2]

Surveillance reports are produced by the Institute of Environmental Science and Research (ESR).

- Reports from 2008 to 2013 are available here: https://surv.esr.cri.nz/surveillance/Meningococcal_disease.php
- Reports from 2014 to present are available here: https://surv.esr.cri.nz/surveillance/annual_surveillance.php

In 2016, 75 cases of meningococcal disease were notified. The notification rate (1.6 per 100,000) was slightly higher than the 2015 rate (1.4 per 100,000; 64 cases). The rate was also a significant decrease from the peak rate (16.7 per 100,000 in 2001) experienced during the New Zealand meningococcal disease epidemic (driven by the B:P1.7-2,4 strain). The 2016 rate is similar to the rate of 1.5 per 100,000 observed in the immediate pre-epidemic years (1989–1990). Figure 1 shows the number of meningococcal disease notifications from 1989 to 2016.

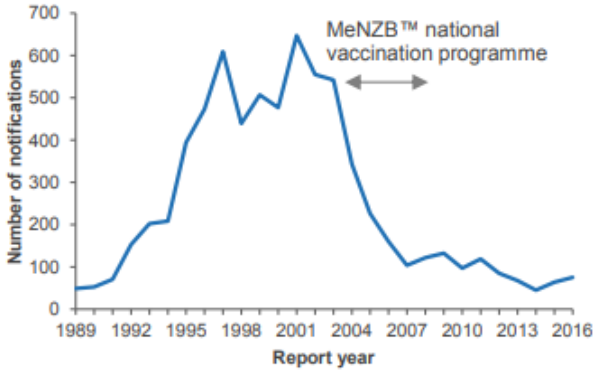

Figure 1: Meningococcal disease notifications by year, 1989–2016

Table 1: Meningococcal disease strain group distribution by year 2012–2016

	2012	2013	2014	2015	2016
Group B	**43**	**30**	**26**	**41**	**47**
B:P1.7-2,4	15	11	13	10	23
Other group B	28	19	13	31	24
Group C	**23**	**17**	**6**	**6**	**8**
C:P1.5-1,10-8	18	15	5	3	4
Other group C	**5**	**2**	**1**	**3**	**4**
Other	**2**	**10**	**4**	**12**	**12**
Group W	0	5	0	6	5
Group Y	2	4	3	6	7
Group E	0	0	1	0	0
Non-groupable	0	1	0	0	0
Total*	**68**	**57**	**36**	**59**	**67**

*Includes total number of laboratory-confirmed cases where strain group was determined.

The highest rate during 2016 was for the <1 year age group (18.6 per 100,000; 11 cases) followed by 1–4 years (6.9 per 100,000; 17 cases). Ethnicity was recorded for all cases. The Pacific peoples ethnic group (4.2 per 100,000; 12 cases) had the highest notification rate followed by the Māori (2.6 per 100,000; 18 cases) ethnic group.

All 75 cases were hospitalised. 2 deaths were reported giving a case fatality rate of 2.7%.

70 cases (93.3%) were laboratory-confirmed and the strain type was determined for 67 cases. These are shown in Table 1 with the majority of cases reporting group B.

Two *N. meningitidis* outbreaks were reported in 2016, involving 4 cases. Although there were increased case numbers for a common strain (B:1.7-2,4) seen in the 15–24 year age group in Dunedin City and Queenstown-Lakes District the case numbers and rates did not meet the threshold to be reported as a community outbreak.

Comments:

[redacted]

The US CDC website states that as part of the licensure process, group B meningococcal vaccines showed that they produce an immune response that suggests the vaccines are protective, but there are limited data available on how well they work to protect against disease. Early data on group B meningococcal vaccines suggest that protective antibodies also decrease fairly quickly after vaccination.

2.2 Bexsero

Approval

Bexsero has been approved in Australia (August 2013), Europe (January 2013), USA (January 2015), Canada (December 2013) and other countries worldwide. The vaccine was introduced to the UK immunisation schedule in September 2015.

Active substances

The following active substances are included:

- Recombinant *Neisseria meningitidis* group B NHBA (Neisseria Heparin Binding Antigen) fusion protein
- Recombinant *Neisseria meningitidis* group B NadA (Neisserial adhesion A) protein
- Recombinant *Neisseria meningitidis* group B fHbp (factor H binding protein) fusion protein
- Outer membrane vesicles (OMV) from *Neisseria meningitidis* group B strain NZ98/254 measured as amount of total protein containing the PorA P1.4

Description of product

Bexsero is a vaccine containing purified, recombinant meningococcal protein antigens expressed and purified in *E. coli,* and Outer Membrane Vesicles (OMV) derived from *N. meningitidis* group B. Immunisation with Bexsero is intended to stimulate the production of bactericidal antibodies that recognise the vaccine antigens NHBA, NadA, fHbp, and PorA P1.4 (the immunodominant antigen present in the OMV component) and are expected to be protective against invasive meningococcal disease (IMD). Meningococci that express these antigens at sufficient levels are susceptible to killing by vaccine-elicited antibodies.

The vaccine antigens present in Bexsero are also expressed by strains belonging to meningococcal groups other than group B. However, data on protection against IMD caused by other groups are limited.

Bexsero is commonly referred to as recombinant Meningococcal group B vaccine (4CMenB).

Indication

Bexsero is indicated for active immunisation against invasive disease caused by *N. meningitidis* group B strains. Bexsero is indicated for vaccination of individuals from 2 months of age and older. The use of Bexsero should be in accordance with official recommendations.

Dose

A summary of the dose recommendations are provided in Table 2.

Table 2: Summary of dose

Age group	Primary immunisation	Intervals between primary doses	Booster
Infants 2 to 5 months	3 doses each of 0.5 mL with first dose given at 2 months of age [a]	Not less than 1 month	One dose between 12 and 23 months
Unvaccinated infants 6 to 11 months	2 doses each of 0.5 mL	Not less than 2 months	One dose in second year of life with interval of at least 2 months between the primary series and booster dose
Unvaccinated children 12 to 23 months	2 doses each of 0.5 mL	Not less than 2 months	One dose with an interval of 12 to 23 months between the primary series and booster dose
Children 2 to 10 years	2 doses each of 0.5 mL	Not less than 2 months	Not established
Adolescents (from 11 years of age and adults)	2 doses each of 0.5 mL	Not less than 1 month	Not established

[a] The first dose should be given at 2 months of age. The safety and efficacy of Bexsero in infants less than 8 weeks of age has not been established. No data are available.

3.0 RISK MANAGEMENT PLAN

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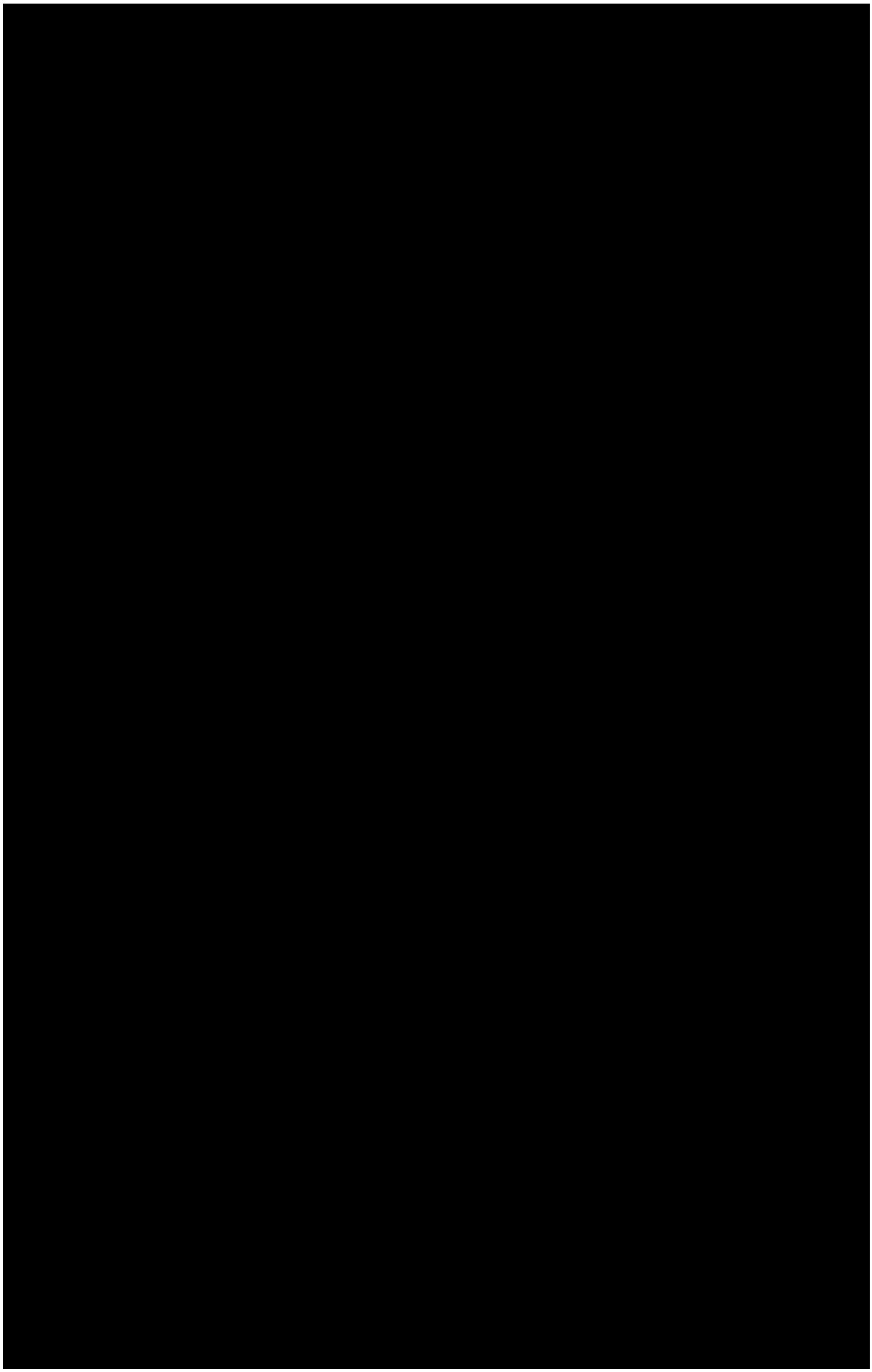

3.4 Bexsero EPAR – Public assessment report

No elements for a public summary were provided so the EPAR (European public assessment report) has been used instead (dated 15 November 2012).
www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002333/WC500137883.pdf

3.4.1 Overview of disease epidemiology

Invasive meningococcal disease occurs worldwide. Each year approximately 1.2 million cases of invasive meningococcal disease are recorded worldwide of which 7000 occur in Europe. The overall incidence in European countries ranges from approximately one to four cases per 100,000 population.

Infants are at the higher risk of acquiring the disease followed by adolescents. In the older age groups the disease is extremely rare. In addition to age, another individual risk factor includes underlying immune deficiencies; the deficiency of complement components are known to determine infection. Crowding and concurrent upper respiratory tract infections might also contribute to acquiring the disease. Despite the availability of medical treatment and effective antibiotics, 8% of European patients die, increasing with age, and up to 11-19% of survivors have lifelong sequelae.

Over 90% of meningococcal meningitis and septicaemia are caused by 5 of the 13 meningococcal serogroups, ie, serogroups A, B, C, W-135 and Y. Serogroup B accounts for a high proportion of meningococcal disease cases in the Americas, Australia and Europe.

The global incidence of serogroup B has been estimated between 20,000 and 80,000 cases per year, accounting for 2000-8000 deaths annually. In Europe, 3406 cases of serogroup B meningitis were reported in 2007.

3.4.2 Meningococcal vaccines

No broadly effective serogroup B meningococcal vaccines are available. Capsular polysaccharide vaccines have been used successfully in preventing disease and limiting epidemics and outbreaks caused by meningococcal serogroups A, C, W135 and Y.

However, the capsular polysaccharide of meningococcal serogroup B is poorly immunogenic in humans, possibly due to similarities in serogroup B carbohydrate moieties to carbohydrates widely distributed in the human body. As a result, research has focused on proteins in the outer membrane of meningococci as potential antigens for candidate vaccines. Serogroup B vaccines based on protein-containing outer membrane vesicles (OMV) have been safe and effective in controlling epidemic disease caused by strains homologues to the vaccine strain in Cuba, Brazil, Chile, Norway and New Zealand. The use of these OMV vaccines to combat serogroup B meningococcal disease has been limited, however, due to the strain-specific nature of the protection and the lack of consistent efficacy in young children.

3.4.3 Summary of treatment benefits

Bexsero is intended for vaccination against group B meningococci. In Europe serogroup B is the most prevalent meningococcal serogroup, with 3406-4819 cases being reported annually between 2003 and 2007 as per European Center of Disease Control surveillance report for 2007. Efficacy was estimated using a serological correlate of protection, serum bactericidal antibodies (SBA). This is considered an acceptable approach. High rates of SBA responses have been demonstrated against all four vaccine components in infants and adolescents following 3 and 2 doses respectively. The SBA titer cut-off used in these studies (≥ 1:4 or 1:5) is considered an acceptable correlate of protection. In addition, these results are supported by data on response rates using a higher cut-off, eg, ≥ 1:8. Also in adults, immune responses to three of the vaccine components have been determined, although the study population was comparatively small.

The proposed amount of antigen in each dose has been demonstrated to be adequate based on interim data from the dose-finding study V72P16 in infants, as well as previous experience with the OMV component alone.

Booster responses to all four antigens were shown at 12 months of age in infants previously vaccinated with 3 doses at least 1 month apart starting at 2 months of age and infants receiving two doses starting at 6 months of age. Data in adolescents supported the presence of immunological memory at 6 months following primary vaccination.

3.4.4 Unknowns in the knowledge about beneficial effects

Although immune responses measured by SBA are expected to be protective, no efficacy data are available. This does not preclude approval based on immunogenicity data. However vaccine effectiveness is required in the post-authorisation phase.

Duration of protection is currently unknown. In infants the antibody levels declined rapidly for the PorA and NHBA antigens, ie, within 6 months of primary vaccination, and within 12 months of booster or primary vaccination in toddlers. The antibody titres in infants against fHbp were also shown to decline although not as much as the PorA titres. The proportion of subjects with SBA titres to fHbp ≥ 1:5 was 50-60% at 12 months after the fourth dose in V72P13E2.

Data was considered limited in adults and lacking in elderly and risk groups, such as immunosuppressed individuals. The company put in place pharmacovigilance activities to address the missing information.

The data obtained in adolescents were from a Chilean population, but considering that the pre-vaccination antibody levels to fHbp, NadA and PorA were similar in the Chilean adolescents as in European adults, the study results were considered relevant to a European population. The immune responses to NHBA in Chilean adults could not be directly compared to European adults but a high proportion of both populations have antibodies to NHBA. The company committed to conduct a study on nasopharyngeal carriage of *N. meningitidis* in young adults (V72_29) that would provide serological relevant for the use in adolescents.

Immunological memory has been demonstrated at 12 months of age following a 3-dose priming schedule in infants 2, 4, 6 or 2, 3, 4 months of age. Memory has not been demonstrated beyond this age group after any other priming schedule or after a longer time period. Data on antibody persistence and immunological memory have not been presented beyond 6 months after the last dose.

The risk for strain replacement could be lower for a protein based meningococcal vaccine compared with the capsular polysaccharide vaccines, as capsular switching is unimportant in this case. The potential protective efficacy against other meningococcal strains is currently unknown, however will be addressed in the epidemiological surveillance to be conducted post-licensure.

3.4.5 Summary of the risk management plan

A summary of the risk management plan (version 4, November 2012) is provided in Table 15.

Table 15: Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risk:		
Fever	Routine PV V72P16 study and paracetamol	Routine minimisation with SmPC and package leaflet for the management of fever: 4.4 Special warnings and precautions for use: "As with many vaccines, health care professionals should be aware that a temperature elevation may occur following vaccination of infants and children (less than 2 years of age). Prophylactic administration of antipyretics at the time and closely after vaccination can reduce the incidence and intensity of post-vaccination febrile reactions. Antipyretic medication should be initiated according to local guidelines in infants and children (less than 2 years of age)."
Important potential risks:		
Guillain-Barré Syndrome	Enhanced pharmacovigilance with questionnaire and adjudication by SMT and post-licensure observational safety surveillance study V72_36OB	None
Acute disseminated encephalomyelitis	Enhanced pharmacovigilance with questionnaire and adjudication by SMT and post-licensure observational safety surveillance study V72_36OB	None
Anaphylaxis and anaphylactic shock	Routine pharmacovigilance Post-licensure observational safety surveillance study V72_36OB	Routine minimisation with SmPC or country specific equivalent labelling with section 4.3 contraindications: "Hypersensitivity to the active substances or to any of the excipients listed" and section 4.4 Special Warnings and Precautions: "As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic

		event following the administration of the vaccine."
Chronic fatigue syndrome	Routine pharmacovigilance	None
Kawasaki disease	Enhanced pharmacovigilance with questionnaire and adjudication by expert panel and post-licensure observational safety surveillance study V72_360B "Plan B" studies: V72_470B	Routine minimisation with SmPC section 4.8 and package leaflet: Undesirable effects: "Vascular disorders Rare: Kawasaki syndrome"
Seizure and febrile seizure	Enhanced pharmacovigilance with questionnaire and adjudication by SMT and post-licensure observational safety surveillance study V72_360B "Plan B" studies: V72_470B and V72_520B V72P16 and V72P13E2 additional data	Routine minimisation with SmPC section 4.8 and package leaflet: Undesirable effects: "Nervous system disorders, Uncommon: seizures (including febrile seizures)"
Decrease immunogenicity after prophylactic use of paracetamol	Routine pharmacovigilance V72P16 study and paracetamol	Routine minimisation with SmPC section 4.5 and package leaflet: "Due to an increased risk of fever, tenderness at the injection site, change in eating habits and irritability when Bexsero was co-administered with the above vaccines, separate vaccinations can be considered when possible. Prophylactic use of paracetamol reduces the incidence and severity of fever without affecting the immunogenicity of either Bexsero or routine vaccines. The effect of antipyretics other than paracetamol on the immune response has not been studied."
Import mission information:		
Vaccine effectiveness	Post-licensure observational vaccine effectiveness study V72_380B study "Plan B" studies: V72_480B and V72_530B	None
Vaccine failure	Enhanced pharmacovigilance with SMT adjudication on pre-establish criteria and research every 6 months in the database V72_380B study "Plan B" studies: V72_480B and V72_530B	None
Vaccine failure	Enhanced pharmacovigilance with SMT adjudication on pre-establish criteria and research every 6 months in the database V72_380B study	None

	"Plan B" studies: V72_480B and V72_530B	
Strain/serotype replacement	Nasopharyngeal Carriage study to define the next step. V72_29 study and V72_380B study "Plan B" studies: V72_480B and V72_530B	None
Elderly	Routine pharmacovigilance	Routine minimisation with SmPC section 4.4 and package leaflet: "There are no data on the use of Bexsero in subjects above 50 years of age."
Immunocompromised subjects	Routine pharmacovigilance Study V72_31 in terminal complement component deficiency subject	Routine minimisation with SmPC section 4.4 Special warnings and precautions for use
Chronic medical condition patients	Routine pharmacovigilance	None
Safety of vaccine during pregnancy	Post-licensure observational pregnancy study (V72_390B) Alternative studies if vaccine uptake is low in planned study centres.	Routine minimisation with SmPC section 4.6 and package leaflet: Pregnancy and breast-feeding. Insufficient clinical data on exposed pregnancies are available. The potential risk for pregnant humans is unknown. Nevertheless, vaccination should not be withheld when there is a clear risk of exposure to meningococcal infection. There was no evidence of maternal or foetal toxicity, and no effects on pregnancy, maternal behaviour, female fertility, or postnatal development in a study in which female rabbits received Bexsero at approximately 10 times the human dose equivalent based on body weights."
Compliance in adolescent and young adult	Routine pharmacovigilance V72P10 including the booster dose	Routine minimisation with stickers for traceability of the 2 doses

4.0 DISCUSSION AND CONCLUSIONS

Epidemiological data from ESR show that the majority of meningococcal disease cases in New Zealand report group B as the strain type. There is currently no meningococcal B vaccine approved for use in New Zealand.

Medsafe is currently evaluating an approval application for Bexsero (recombinant Meningococcal group B vaccine) with the intent for this vaccine to be considered as part of the 2019 immunisation schedule review. Bexsero has been approved in other countries including Australia (August 2013), Europe (January 2013), USA (January 2015) and Canada (December 2013). The vaccine was introduced to the UK immunisation schedule in September 2015.

Due to previous interest with another meningococcal B vaccine product (MeNZB) when it was used during 2004 to 2008, Medsafe considered it appropriate to request an RMP for Bexsero. The RMP provided to Medsafe is version 4, November 2012. Fever was the only identified risk with a number of other important potential risks and missing information. As stated in the pharmacovigilance guidelines, the company will be required to submit PBRERs for Bexsero if it is included as a funded vaccine on the immunisation schedule.

5.0 ADVICE SOUGHT

The Committee is asked to advise on the following:

- Are any changes required to the RMP?
- Are there any elements that require clarification or further information from the company?
- Are there any actions required should this vaccine be funded (eg, additional monitoring and/or reporting, information for consumers and/or healthcare professionals etc.)?

6.0 ANNEXES

1. Risk management plan for Bexsero or multicomponent meningococcal B (4CMenB) vaccine version 4.
2. Medsafe clinical evaluation report.

7.0 REFERENCES

1. Ministry of Health. *Meningococcal disease (including meningitis)*. 19 January 2018 [Accessed 13 March 2018]; Available from: www.health.govt.nz/your-health/conditions-and-treatments/diseases-and-illnesses/meningococcal-disease-including-meningitis.
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