Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Multi-Component Meningococcal B vaccine

Proprietary Product Name: Bexsero

Sponsor: Novartis Vaccines and Diagnostics Pty Ltd

October 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of submission:	New Chemical Entity
Decision:	Approved
Date of decision:	9 August 2013
Active ingredients:	*Neisseria meningitidis* Group B Factor H Binding Protein fusion protein, *Neisseria meningitidis* Group B Neisseria Adhesin A protein, *Neisseria meningitidis* Group B Neisseria Heparin Binding Antigen fusion protein, *Neisseria meningitidis* serogroup B outer membrane vesicles
Product name:	Bexsero
Sponsor's name and address:	Novartis Vaccines and Diagnostics Pty Ltd 54 Waterloo Road North Ryde NSW 2113
Dose form:	Suspension for injection
Strength:	One dose (0.5 mL) contains 50 µg of each of the 3 recombinant *Neisseria (N.) meningitidis* Group B proteins and 25 µg outer membrane vesicles
Container:	Prefilled syringe with or without needle
Pack sizes:	1 (with or without needle) and 10 (without needle)
Approved therapeutic use:	Bexsero is indicated for active immunisation against invasive disease caused by *N. meningitidis* group B strains. See Pharmacology for information on protection against specific group B strains. Bexsero is indicated for vaccination of individuals from 2 months of age and older.
Route of administration:	Intramuscular injection
Dosage (abbreviated):	Infants aged 2 months to 5 months: three doses, each of 0.5 ml, with an interval of at least 1 month between doses. A booster dose is recommended between 12 months and 23 months of age. Unvaccinated infants aged 6 months to 11 months: two doses of 0.5 mL with an interval of at least 2 months between doses. A booster dose is recommended in the second year of life. Unvaccinated toddlers and children aged 12 months to 10 years: two doses of 0.5 mL with an interval of at least 2 between doses. The need for a booster dose after this vaccination schedule has not been established.

	Individuals 11 years to 50 years of age: two doses, each of 0.5 mL, with an interval of at least 1 month between doses. The need for a booster dose after this vaccination schedule has not been established. Individuals above 50 years of age: There are no data in individuals above 50 years of age.
ARTG numbers:	190719 and 190718

Product background

This AusPAR describes the application by Novartis Vaccines and Diagnostics Pty Ltd (the sponsor) to register Bexsero meningococcal B vaccine for active immunisation against invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* (*N. meningitidis*) serogroup B strains in individuals from 2 months of age and older.

This vaccine is a liquid suspension adsorbed on aluminium hydroxide ($Al(OH)_3$) and presented as a mono-dose (in a glass syringe) ready for intramuscular (IM) injection. The composition of the vaccine is shown in Table 1.

Table 1. Composition of Bexsero vaccine

Active ingredients	Other ingredients
N. meningitidis Group B Neisseria Heparin Binding Antigen fusion protein (961c purified antigen) *N. meningitidis* Group B Neisseria Adhesin A protein (936-741 purified antigen) *N. meningitidis* (Group B Factor H Binding Protein fusion protein) ΔG287-953 purified antigen Outer membrane vesicles (OMV) from *Neisseria meningitidis* group B strain NZ98/254 measured as amount of total protein containing the PorA P1.4	Aluminium hydroxide NaCl Histidine Water for injection

The proposed vaccine is a multi-component meningococcal B vaccine composed of three purified recombinant *N. meningitidis* serogroup B protein antigens: Neisseria adhesin A (NadA or 961c) as single protein, Neisseria Heparin Binding Antigen (NHBA or 287) as fusion protein, factor H Binding Protein (fHBP or 741) as fusion protein, and Outer Membrane Vesicles (OMV) derived from *N. meningitidis* serogroup B strain NZ 98/254, with the protein PorA P1.4 as the main antigen (as described in Table 1). A 0.5 mL dose of the vaccine contains 50 µg of each recombinant protein and 25 µg of the OMV measured as total protein amount.

Bexsero (also called 4CMenB or rMenB+OMV NZ) was developed as a vaccine to prevent meningitis and sepsis caused by *N. meningitidis* serogroup B. Infants and children aged 6 months to 2 years are at greatest risk of this lethal disease. In Australia, the majority of cases of invasive meningococcal disease (IMD) have been shown to be caused by *N. meningitidis* serogroup B. According to the National Notifiable Diseases Surveillance System there were 259 notifications of IMD in Australia in 2009, representing notification rates of 1.2 per 100,000. Eighty-six per cent of IMD notifications (224) in 2009 had

serogroup data available, of which 88% (197) were caused by serogroup B organisms. The highest rate for serogroup B infection in 2009 was in the 0-4 years age group (5.2 per 100,000 population) followed by a peak in children from 15-19 years of age (2 per 100,000 population) (Communicable Diseases Intelligence Vol 35 Number 2, June 2011). There is currently no vaccine available in Australia for the prevention of disease caused by *N. meningitidis* serogroup B.

Regulatory status

Bexsero received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 14 August 2013.

At the time this application was considered by the TGA, a similar application had been approved in the European Union (EU) and was under consideration in Canada.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Bexsero contains four components that might be considered drug substances: 3 recombinant *N. meningitidis* Group B proteins:

- Neisseria Heparin Binding Antigen (NHBA) fusion protein
- Factor H Binding Protein (fHBP) fusion protein
- Neisseria Adhesin A (NadA) protein

and

- Outer membrane vesicles (OMV) from *N. meningitidis* serogroup B strain NZ 98/254.

The NHBA fusion protein (Protein 287-953) is a product of Neisserial Heparin Binding Antigen, a primary antigenic component, and an accessory protein (953) that enhances the immunogenicity of its fused counterpart. The fusion protein is expressed via bacterial fermentation by standard recombinant deoxyribonucleic acid (DNA) technology methods in *Escherichia coli (E. coli)* using a plasmid vector system.

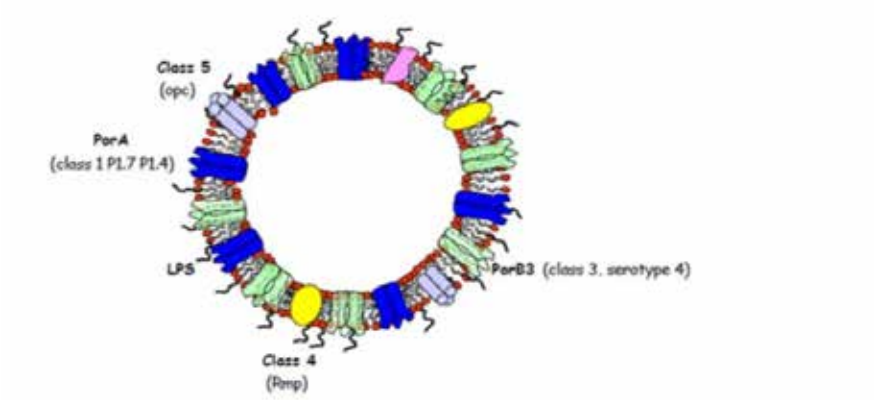
The fHBP fusion protein (Protein 936-741) is a product of Factor H Binding Protein (the primary antigenic component) and an accessory protein (936) that enhances the immunogenicity of its fused counterpart. The fusion protein is expressed via bacterial fermentation by standard recombinant DNA technology methods in *E. coli* using a plasmid vector.

NadA (Protein 961c) is a fragment of Neisseria adhesin A, a surface-exposed oligomeric protein belonging to the oligomeric coiled-coil adhesin (OCA) family. NadA is a meningococcal adhesin molecule involved in binding to epithelial cells. This antigen is also expressed via bacterial fermentation by standard recombinant DNA technology methods in *E. coli* using a plasmid vector system.

The primary antigenic components of the three recombinant proteins were identified by reverse vaccinology.

Outer membrane vesicles are extracted via detergent from the bacterial membrane of *N. meningitidis* serogroup B strain NZ98/254. The primary immunogenic components of the OMV are the outer membrane proteins (OMPs) and the membrane-bound lipopolysaccharides (LPS). OMVs are complex mixtures of lipids, OMPs, and peri-plasmic components. A diagram of an intact OMV, with selected major OMPs and LPS embedded in the vesicular membrane, is provided in the diagram below.

Figure 1. Diagram of an OMV Particle



Legend: PorA (blue), the Class 5 Protein (Light-Grey Cylinders) the Class 4 Protein (Yellow Egg-forms) and PorB3 (the other green components). LPS protrudes out of the membrane.

The outer membrane protein PorA P1.4 is considered the main antigen of OMV.

Manufacture

The manufacturing process for each recombinant protein is divided into three separate stages:

- fermentation,
- isolation, and
- purification.

During the fermentation step, *E. coli* cells containing the recombinant plasmids encoding each antigen are expanded. The recombinant proteins are expressed and harvested.

After the broth has been harvested, the bacteria are separated from the supernatant via centrifugation. The recombinant proteins are isolated via centrifugation and filtration steps.

The last series of steps in bulk manufacture of the three recombinant antigens are the purification steps. Bulk concentrates are filled into sterile screw-capped polyethylene terephthalate glycol copolyester (PETG) bottles.

The manufacturing process for OMV is divided into three main phases:

- fermentation and harvest,
- purification, and
- sterile filtration.

During the fermentation step culture expansion occurs. After fermentation the bacterial suspension is concentrated and inactivated. The inactivated suspension undergoes centrifugation to remove cellular debris and the supernatant is recovered to yield the crude OMV intermediate, which is then purified.

The filtered pre-bulk is sterile filtered to yield the OMV sterile bulk concentrate.

Cell banking processes are satisfactory. All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Physical and chemical properties

The purified recombinant proteins in buffer solution are described as a colourless clear liquid essentially free from visible particulates.

The OMV drug substance is a sterile suspension of OMV and OMV fragments that are extracted from the bacteria by the use of the detergent and then suspended. Outer membrane vesicles are a complex mixture of lipid, outer membrane proteins, periplasmic components and cytoplasmic proteins.

The relevant biological properties of the four drug substances are derived from their capacity to act as immunogens in the formulated vaccine and elicit appropriate protective responses in vaccinees.

The elimination of product-related impurities from the drug substances is satisfactorily addressed in the data.

Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use, are described for the three recombinant protein drug substance bulk concentrates and the OMV concentrated bulks.

Appropriate validation data have been submitted in support of the test procedures for all antigens.

Stability data have been generated under real time to characterise the stability profile of the drug substances and to establish shelf lives.

Drug product

Description and composition

Bexsero multi-component meningococcal B vaccine (recombinant, adsorbed) suspension for injection 0.5 mL pre-filled syringe contains three recombinant proteins, OMV and the excipients aluminium hydroxide ($Al(OH)_3$), sodium chloride, sucrose, histidine and water for injection.

There are no overages used in the manufacture of this vaccine. An over-fill of 0.1 mL is included in the syringe to ensure that 0.5 mL can be withdrawn. The vaccine is supplied in a 1 mL hydrolytic glass pre-filled syringe without a pre-affixed needle. Syringes are sealed with a bromobutyl rubber plunger stopper and tip cap.

Manufacture

The manufacturing process for the drug product involves formulation of the drug substances with $Al(OH)_3$ and buffers, followed by aseptic filling, visual inspection and packaging.

The formulated bulk is aseptically filled into unit dose syringes under Class A Laminar Air Flow (LAF) in a Class B room. Filled syringes are inspected for defects prior to labelling; the syringes are then labelled and packaged for distribution.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product, have been provided for the final bulk, filled and packaged product.

The proposed test methods and specifications are different from those proposed in the original data. In particular, the test methods and specifications for endotoxin and immunogenicity (potency) were significantly improved in response to the evaluation process. The sponsor considers that the proposed endotoxin specification is clinically qualified and provides assurance that manufactured lots will be representative of lots used in clinical studies and shown to be safe (see discussion under *Summary of evaluation and issues of importance* below). Because of the potentially pyrogenic nature of the OMV component of the vaccine, the specifications contain a modified *in vivo* pyrogens test in addition to the endotoxin test. The sponsor believes that this test has the capacity to register the presence of non-endotoxin pyrogens in the product.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. The proposed shelf life is 2 years when stored at 2-8 °C protected from light.

The stability data originally submitted to support the proposed shelf-life contained results of potency and endotoxin testing conducted by methods that were considered unacceptable and were replaced during the evaluation process by improved methods. This means that the stability data is incomplete in that it does not contain real-time potency and endotoxin results obtained by (what are now) the current test methods.

The sponsor proposes that the finding that a number of batches of vaccine used in clinical studies were clinically effective when used at times in excess of 24 months after manufacture should be considered to justify the proposed shelf-life until appropriate stability data generated by the new potency and endotoxin tests are available. This proposal is conditionally supported with the requirements that the sponsor provides TGA with stability data that will become available from ongoing studies and acknowledges the obligation to notify TGA of any results in ongoing stability studies that could indicate a trend towards diminished potency over the 24 month storage period. A recommendation is made (see below) of an additional condition of registration that addresses the stability testing program to be applied should approval of this application be granted.

Biopharmaceutics

Biopharmaceutic data are not required for this product.

Advisory committee considerations

This application was considered at the 150th meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM). The PSC recommendation was as follows:

1. The PSC endorsed all the questions raised by the TGA in relation to the quality and pharmaceutic aspects of the application to register Bexsero suspension for injection. In particular, the PSC supported the questions in relation to the introduction of a final sterilisation step prior to filling.

2. The PSC advised that the sponsor should ensure that stability trials, including future follow-up trials and batch analyses, include batches with *N. meningitidis* serogroup B OMV manufactured at the two nominated sites.
3. The PSC:
   - Considered the retrospective use of the proposed assay for potency and endotoxin unacceptable.
   - Was concerned that *N. meningitidis* serogroup B OMV included in the formulation, which has an inherent pyrogenic activity, is expected to elicit response. The PSC noted that the endotoxin antigen is adsorbed onto $Al(OH)_3$ used as an adjuvant in the formulation.
   - Agreed that it was difficult to assess the correlation between the *in vitro* tests and clinical efficacy of the product.
4. The PSC recommended that the attention of the clinical Delegate and the ACPM be drawn to these issues and that acceptance of the products should be made on clinical grounds.

   There was no requirement for this submission to be reviewed again by the PSC before it was presented for consideration by the ACPM.

Quality summary and conclusions

Summary of evaluation and issues of importance

The administrative, product usage, chemical, pharmaceutical, and microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

This application was originally submitted in 2011. A TGA consolidated request for further information after the first round evaluation was sent to the sponsor on 30 April 2012. Along with requests for clarifications, serious concerns were raised about two aspects of the quality data. These two aspects of concern related to the monitoring of bacterial endotoxins and the design and efficacy of the potency test conducted on the final product.

As a result of representations made by the sponsor, a "clock-stop" was implemented to allow the sponsor time to develop an alternative finished product potency assay. This time was also used to implement improvements to the bacterial endotoxins testing procedures.

The sponsor subsequently submitted details of a completely new final product potency test and a modified set of bacterial endotoxins testing procedures. Replacement of such a crucial test as the potency test at this late stage in the process of development and registration of a vaccine raises significant challenges.

The issues identified were considered in a separate TGA evaluation and questions arising out of that evaluation sent to the sponsor. After considering the responses, the issues identified below remain as outstanding aspects of the quality data that were brought to the Delegate's attention:

Issue 1: Labelling

The sponsor has requested a Section 14 exemption to the TGA labelling order (Therapeutic Goods Order (TGO) 69 Clause 3(2)(b) & (c)) for the syringe label. This will be actioned by the evaluator should approval of the application be granted.

Issue 2: Modified potency and bacterial endotoxins assays

Retrospective application of the modified potency assay and bacterial endotoxins assay to the quality data package presents problems that have been identified in the evaluation process and have led to the absence of data that would, in other circumstances, be expected to be included in the dossier. The package does not contain batch analysis data of lots tested to the final specifications nor does it contain real-time stability data showing compliance with the final specifications for even a small proportion of the proposed shelf life. The sponsor has addressed some of these problems by making reference to clinical data and has made the following assertions, the confirmation of which will require clinical and toxicological comment:

1. Vaccine lots used beyond their proposed 24 month shelf-life have been shown to be clinically effective:
   - The reference vaccine used in the development of the potency assay was still clinically active beyond 24 months after manufacture: this Lot was manufactured (formulated) according to the commercial manufacturing process in 2010 and was chosen as the reference standard for the potency assay. This lot was administered in clinical Study V72_41 and immunogenicity data presented indicated that the lot showed an acceptable protective immune response.
   - Another Lot was used at a median age of 27 months in clinical Study V72P16 and gave an acceptable protective immune response.
   - A further Lot had a median age of 29 months when used in clinical Study V72_41 and gave an acceptable protective immune response.

These assertions in relation to the clinical data are used to support the proposed 24 month shelf life for Bexsero in the absence of a stability data package that contains the results of testing vaccine lots to the current release and stability specifications.

2. Clinical vaccine was potent at half-dose, based on the fact that a Lot used at half-dose in clinical Study V72P16 was demonstrated to be non-inferior to a full dose.

This observation is used to support the proposed release and stability specifications for potency (or immunogenicity) tested by the potency assay.

Note: The evaluation of Studies V72P16 and V72_41 in the context of these claims was evaluated in a supplementary clinical evaluation report (see *Supplementary Clinical Evaluation*, below).

Issue 3: Bacterial endotoxins

While the methodology of testing the final product for bacterial endotoxins is now considered acceptable and the data confirm consistency between clinical and commercial lots of vaccine for this test, the proposed specification limit applied in conjunction with the modified *in vivo* rabbit pyrogens test requires comment. This limit is orders of magnitude higher than limits applied to most paediatric vaccines, which are typically of the order of hundreds of IU/mL. The endotoxin content of Bexsero derives from the OMV component and is therefore an intrinsic part of the formulation.

In response to questions during the evaluation process about the safety of batches of vaccine with such levels of bacterial endotoxins the sponsor has sought to justify the proposed specification by reference to safety profiles of batches used in clinical studies. Evaluation of such safety data will require clinical and toxicological evaluation and comment.

Conclusions and recommendations

All issues identified by the sterility, viral safety and container safety evaluators were satisfactorily resolved.

The unusual history of this application has resulted in a quality data package that is not as comprehensive as should be required to justify an unqualified recommendation for approval. The package does not contain batch analysis data of lots tested to the final specifications nor does it contain real-time stability data showing compliance with the final specifications for even a small proportion of the proposed shelf life. However, the sponsor has sought to compensate for these deficiencies to some degree by reference to clinical trials data identified in Issue 2 above.

Notwithstanding the deficiencies in the quality data, the evaluators considered that the substantial package of data that has been provided by the sponsor contains no indication that commercial batches of Bexsero would not meet appropriate quality standards or not be of equivalent efficacy to batches used in clinical trials.

Subject to appropriate clinical and toxicological comment on matters identified in Issues 2 and 3 above, the chemistry and quality evaluators recommend that Bexsero multi-component meningococcal B vaccine (recombinant, adsorbed) suspension for injection 0.5 mL pre-filled syringe should be considered for approval if the additional conditions of registration described below are imposed.

Approval of this application, if granted, should be conditional on the following:

- An agreed timetable for the sponsor to provide, at the earliest opportunity, finished product stability data for the 5 recently produced commercial batches of Bexsero currently on stability testing (referred to in correspondence dated April 2013), starting with the 6 months time point followed by updates of the results at each testing time-point until the data package is considered adequate. Data on these batches of Bexsero should include identification and manufacturing dates of the drug substance lots used in their formulation.
- Before release of the first batch of Bexsero onto the Australian market, the sponsor should provide TGA with:
  - results of testing of three commercial batches of Bexsero tested at release to the current finished product specifications (that is, including modified LAL, potency and visible particles) and evidence of release by the regulatory agency acting for the country of origin.
  - an assurance that the reference standard used in immunogenicity testing of the batch has been appropriately clinically qualified.

Standard Lot/Batch release and Certified Product Details (CPD) requirements should also be applied as conditions of registration if this application is approved.[1]

[1] Details of these are beyond the scope of the AusPAR.

III. Nonclinical findings

Introduction

General comments

The sponsor has applied to register a multicomponent meningococcal serogroup B vaccine (Bexsero). No other vaccines are currently registered for protection against serogroup B strains of *N. meningitidis*.

The vaccine (0.5 mL dose) contains 50 µg each of 3 recombinant protein antigens, 2 of which are fused to accessory proteins (287-953 and 936-741). The protein antigen sequences were derived from 3 *N. meningitidis* strains, NZ98/254 (antigen 287), strain 2996 (antigens 953, 936 and 961c) and strain MC58 (antigen 741). In addition, the vaccine contains OMVs from *N. meningitidis* serogroup B strain NZ98/254 (B:4:P1.7-2,4), designated OMV/NZ, containing 25 µg of OMV (PorA1.4) protein, the immunodominant protein, and other minor proteins. This strain was responsible for a recent outbreak in NZ. The OMVs preserve the native complex antigen composition of the subcapsular cell surface of *N. meningitidis*. The vaccine is adjuvanted with $Al(OH)_3$.

The proposed dose of 50 µg for each of the 3 protein antigens in Bexsero and 25 µg for the OMV component (total protein 175 µg) is relatively high. The elemental aluminium content of Bexsero of 0.5 mg per 0.5 mL dose is also relatively high, although within FDA[2] and WHO[3] regulatory limits.

In support of this application, the sponsor submitted the following nonclinical data:

- Primary pharmacology studies: 3 studies (2 in non-human primates) and 5 published papers (4 reviewed);
- Single and repeated dose toxicity: 3 studies;
- Reproductive and developmental toxicity: 3 studies;
- *In vitro* toxicity: 1 study.

The nonclinical studies were in general accordance with the relevant European[4] and World Health Organization (WHO)[5] vaccine guidelines. The clinical formulation of the vaccine (Bexsero) was tested in the pivotal toxicity and reproductive and developmental toxicity studies, which included related, developmental vaccines, including an early candidate vaccine containing antigen 287 and OMV derived from Norwegian serogroup B strain H44/76 (denoted OMV-NW), and an OMV-NZ vaccine (MeNZB).

Pharmacology

Primary pharmacology

The immunogenicity of individual antigenic components and the full clinical formulation was assessed in mice, guinea pigs, juvenile baboons and infant rhesus macaques. Immunogenicity was also assessed in the toxicology studies in rabbits. The studies measured antibody formation by enzyme-linked immunosorbent assay (ELISA) and serum bactericidal activity (SBA) following single and repeated doses. A naturally occurring SBA

[2] US Code of Federal Regulations 610.15(a).
[3] Who Technical Report Series no. 595. Immunological adjuvants- Report of a WHO Scientific Group.
[4] Note for Guidance on Preclinical Pharmacological Testing of Vaccines (CPMP/SWP/465/95).
[5] WHO Technical report no. 927, 2005: WHO Guidelines on Nonclinical Evaluation of Vaccines.

≥ 1:4 has been correlated with protection against serogroup B and serogroups A/C in humans (WHO 1999[6], 2011[7]). In addition, published studies in infant rats assessed the ability of antigenic components of Bexsero to confer passive protection against bacteraemia caused by various serogroup B strains of *N. meningitidis*.

Table 2. Bexsero doses in immunogenicity studies

Species	Treatment (dose route)	Dose of 287-953, 936-741, and 961c each	Dose of OMV	Dose of $Al(OH)_3$	Dose volume	Study no.
Mouse	Days 0, 21, 35 (IP)	20 µg	10 µg	600 µg	200 µL	263903-01
Guinea pig	Days 0, 21, 35, 48 (SC)	25 µg	12.5 µg	750 µg	250 µL	
Juvenile (9-20 months) baboon	Day 0, months 1 + 2 (IM)	50 µg	25 µg (NW)	1.5 mg	0.5 mL	283886-01
Infant (2-3 months) rhesus macaque	Day 0, weeks 4 and 18 (IM)	50 µg	25 µg	1.5 mg	0.5 mL	283887-01
Human	2-4 doses at monthly or greater intervals (IM)	50 µg	25 µg	1.5 mg	0.5 mL	---

The studies in mice demonstrated that 3 intraperitoneal (IP) injections of the individual antigenic components of Bexsero, adjuvanted with $Al(OH)_3$, resulted in SBA titres against the 4 diverse *N. meningitidis* serogroup B strains 2996, MC58, NZ98/254, and H44/76. The aluminium-adjuvanted fusion proteins were found to cause greater and broader SBA against the tested serogroup B strains than the individual antigens. The clinical formulation of Bexsero was also tested and found to induce significant SBA titres against all four of the serogroup B strains tested.

The immunogenicity of the clinical formulation was investigated in guinea pigs administered a total of 4 subcutaneous (SC) injections of the clinical formulation. Serum bactericidal activity titres against the serogroup B strains 2996, MC58, and H44/76 were observed in all animals.

Overall, the studies indicated that immunisation, whether with individual protein antigens, protein-protein fusions or the Bexsero vaccine formulation with and without OMV/NZ, was immunogenic in mice and guinea pig models.

The study in juvenile baboons evaluated the immunogenicity of two recombinant *N. meningitidis* group B vaccines consisting of 3 MenB recombinant antigens formulated with $Al(OH)_3$, or the 3 MenB antigens formulated with OMVs from the Norwegian strain H44/76, and $Al(OH)_3$. Three consecutive doses of the two formulations containing recombinant meningococcal serotype B (rMenB) proteins (50 µg per dose) elicited bactericidal antibodies against a panel of 15 diverse MenB strains. Three intramuscular (IM) doses with either rMenB or rMenB+OMV/NW vaccine were immunogenic, inducing high geometric mean bactericidal titres (GMTs) and percentages of positive SBA. A second primate study was conducted in infant rhesus macaques immunised IM (x 3, 0.5 mL per dose) with the clinical dose of Bexsero. The study demonstrated that Bexsero (3 x IM immunisations) elicited bacterial antibodies against genetically diverse MenB strains.

[6] World Health Organization. Standardization and validation of serological assays for the evaluation of immune responses to *Neisseria meningitides* serogroup A/C vaccines. March 1999. Report WHO/V&B/99.19.
[7] World Health Organization. Meningococcal vaccines: WHO position paper. *Weekly epidemiological record.* November 2011:86: 521-540.

Overall, treatment with one quarter of the clinical Bexsero dose in mice or guinea pigs or with the clinical dose in rabbits and non-human primates was found to be immunogenic. Active protection was not assessed due to the lack of animal models of infection for *N. meningitidis*, a human-specific pathogen.

A number of publications reported that passive protection against *N. meningitidis* bacteraemia was conferred in infant rats by IP treatment with antisera from mice or guinea pigs vaccinated with individual or combined antigens from the vaccine (Comanducci *et al.,* 2002[8], Masignani *et al.*, 2003[9], Giuliani *et al.*, 2006[10]).

No dose range-finding immunogenicity studies were submitted. It was stated that the clinical doses of the 3 protein antigens were selected on the basis of studies in mice, which showed that a dose of 1-10 µg of each antigen was required for a robust and persistent immune response, together with a scale-up factor of approximately 10.

Safety pharmacology

No dedicated safety pharmacology studies were submitted. Some safety pharmacology parameters, such as body temperature, respiration and heart rates, were investigated in the toxicity studies (see *Toxicology*).

Toxicology

Table 3. Bexsero doses in toxicity studies

Study	Treatment days	Dose of 287-953, 936-741, and 961c each	Dose of OMV	Dose of $Al(OH)_3$	Study no. (date)
Rabbit single and repeat-dose toxicity study	1, 15, 29, 43, 57	50 µg 100 µg	25 µg (NW/NZ) 25 µg (NW)	1.5 mg 3 mg	1228-102 (2005)
Rabbit reproductive + developmental toxicity (dose-finding)	Premating 1, 15, 29, GD 7, 20	50 µg 100 µg	25 µg (NZ) 50 µg (NZ)	1.5 mg 3 mg	UBA00041 (2008)
Rabbit reproductive + developmental toxicity (pivotal)	Premating 1, 15, 29, GD 7, 20	50 µg	25 µg (NZ)	1.5 mg	UBA00044 (2009)
Human	2-4 doses at monthly or greater intervals	50 µg	25 µg (NZ)	1.5 mg	---

Single and repeat dose toxicity

The potential toxicity of the clinical formulation (Bexsero) and related vaccine formulations was assessed in a combined single and repeat dose toxicity study (1228-102) in rabbits. Two studies (CIQ/007 and CIQ/006) were conducted with an earlier version of Bexsero. Local tolerance was assessed in the repeat-dose toxicity studies (refer to *Local Tolerance* below).

No adverse effects were observed in any of the studies when either rMenB protein antigens or the clinical formulation was administered IM, including in two studies where double the protein antigen dose intended for clinical use in humans was used.

[8] Comanducci M *et al.* NadA, a novel vaccine candidate of Neisseria meningitidis. *J Exp Med* 2002:195(11):1445-1454.
[9] Masignani V *et al*. Vaccination against Neisseria meningitidis using three variants of the lipoprotein GNA1870. *J Exp Med* 2003:197(6)789-799.
[10] Giuliani MM *et al.*. A universal vaccine for serogroup B meningococcus. *PNAS* 2006:103(29):10834-10839.

The repeat dose study involved administration of 5 IM doses of the Bexsero clinical formulation and other rMenB vaccine formulations to male and female rabbits. The single dose toxicity study illustrated that the vaccine formulation was immunogenic 14 days after a single dose administration. The repeat dose study dosing schedule exceeded the clinical schedule in humans by at least 1 dose and each dose was 2 weeks apart, compared to the intended clinical dosing schedule of at least 1 month apart.

In some studies at various time points and across treated groups, there were small, statistically significant elevations in mean fibrinogen (<2-fold above the control value) and globulin values and in leukocyte and neutrophil counts, which were consistent with an immune and/or inflammatory response. Small increases in creatinine kinase and lactate dehydrogenase were reflective of mechanical injury at the injection site. The haematological changes normalised within 14 days post-dose. There were no indications of systemic toxicity.

Each clinical dose of Bexsero administered IM to rabbits (males 2.3-3.8 kg body weight and females 2.6-3.8 kg body weight) represented approximately 10 times the dose proposed in 40 kg adolescents and 1.3-2.1 times the dose proposed in infants (5-10 kg body weight).

Endotoxin

An endotoxin release specification has been proposed for Bexsero vaccine. Most endotoxin is removed by extraction during vaccine manufacture, however some LPS is required to maintain protein antigen stability in the OMVs and it also serves as an adjuvant. Meningococcal endotoxin (or lipooligosaccharide (LOS), here referred to as LPS) is a major virulence factor in *N. meningitidis* infections and high levels can be toxic and contribute to septic shock. Purified meningococcal LPS at a dose of 10 ng has been reported to cause a significant body temperature increase (<1°C) in rabbits when injected IV (Gotschlich *et al.*, 1969[11]). Rosenqvist *et al.* (1998[12]) reported an approximately 50-fold reduction in pyrogenicity in rabbits when LPS was incorporated in OMVs and a further 4-fold reduction when the OMVs were adsorbed to $Al(OH)_3$. Shi *et al.* (2000[13]) reported that systemic effects of a 15 µg/kg SC dose of *E. coli* endotoxin in rats, measured as increases in serum tumour necrosis factor alpha (TNFα) and interleukin (IL) 6 (IL-6), were abolished by adsorption to $Al(OH)_3$ adjuvant.

In the pivotal single and repeat-dose toxicity study (no. 1228-102), New Zealand White (NZW) rabbits were administered (by IM injection) the clinical dose of Bexsero vaccine (lot no. MB3OMZ/03V) or 2 clinical doses of MenB+OMV NW vaccine (lot no. MB3OMW/03V), providing respective endotoxin levels of 3593 and 3972 IU/mL. The vaccine clinical dose was administered to rabbits weighing 2.3-3.8 kg in this study, which is 1.3-2.1 times the dose in a 5 kg human infant on the basis of bodyweight. There were no treatment-related effects on rabbit rectal temperatures; however the measurement time at approximately 48 h post-dose was not optimal. A published study with another *N. meningitidis* serogroup B OMV vaccine, in which rabbit body temperatures were recorded continuously, reported that body temperature peaked about 4 h post-dose (Kaaijk *et al.*, 2011[14]). In response to a TGA request for information, the sponsor stated that in more recent toxicity studies, body temperatures were measured closer to the time of dosing.

[11] Gotschlich *et al.* Human immunity to the meningococcus IV. Immunogenicity of group A and group C polysaccharides in human volunteers. *J Exp Med* 1969:129: 1367-1384.
[12] Rosenqvist E *et al*.. Effect of aluminium hydroxide and meningococcal serogroup C capsular polysaccharide on the immunogenicity and reactogenicity of a group B Neisseria meningitidis outer membrane vesicle vaccine. *Dev. Biol. Stand*. 1998:92: 323-333.
[13] Shi Y *et al.*. Detoxification of endotoxin by aluminium hydroxide adjuvant. *Vaccine* 2000:19: 1747-1752.
[14] Kaaijk P *et al.*. Nonclinical vaccine safety evaluation: advantages of continuous temperature monitoring using abdominally implanted data loggers. *J App Toxicol* 2011 (wileyonlinelibrary.com) DOI10.1002/jat.2720.

The nonclinical data suggest that the endotoxin in Bexsero may have some residual pyrogenicity and vaccine pyrogenicity will require detailed clinical evaluation, particularly in infants.

Local tolerance

Local tolerance was assessed in the repeat-dose toxicity studies by macroscopic and microscopic examinations and Draize scores of skin reactions. It was also assessed by skin observations in the reproduction and developmental toxicity study. Injection site reactions, observed in both control and treated rabbits, were marginally increased in incidence and severity in treated rabbits and were characteristic of an aluminium-adjuvanted vaccine (for example, granulomata). Injection site histopathology showed partial recovery 14 days post-dose. All Draize scores were low and within acceptable limits.

In vitro toxicity studies

A number of *in vitro* studies, combined into a single report (RT 10/281), investigated potential effects of the vaccine proteins and OMVs that might be related to the pathogenicity of *N. meningitidis*. The studies tested potential effects on (Part A) binding and cytotoxicity to primary human endothelial cells (human umbilical vein endothelial cells, HUVECs), cell monolayer permeability, cytokine production by HUVECs, (Part B) prothrombin time (PT) and activated partial thromboplastin time (aPTT) in human plasma, cytokine induction in human whole blood, enzymatic (procoagulant) activity of activated protein C, and platelet activation and platelet-leukocyte aggregation. In some studies the potential effects of the vaccine recombinant proteins were also investigated using knock-out mutant strains of *N. meningitidis*.

Small, significant binding of vaccine proteins to HUVECs *in vitro* was observed, and OMV NZ binding occurred at 10-20 µg, however no cytotoxicity was evident. These findings are unlikely to have any toxicological significance.

The vaccine recombinant proteins did not increase expression of TNFα or IL-1β in HUVECs but did increase expression of IL-6 and IL-8 when adsorbed to aluminium, although the increases were comparable to those with the registered aluminium-adjuvanted vaccines Prevnar and Infanrix. The vaccines Act-HIB and Pneumovax 23, which lack aluminium, had no effect. Expression of IL-6 and IL-8 by HUVECs was also increased by culture with wild-type *N. meningitidis*; however, expression was unaffected in knock-out mutants. Outer membrane vesicles NZ greatly increased expression of IL-6 and IL-8, and the addition of the vaccine proteins had little extra effect. Vaccine recombinant proteins modestly increased expression of IL-1β, IL-6, IL-8, interferon gamma (IFN-γ) and TNF-α in cultured human whole blood, and the increases were similar to those observed with the registered vaccines Prevnar, Infanrix, Act-HIB and Pneumovax 23. Substantial increases in these cytokines were induced by OMV NZ; in fact the increases were significantly higher than those induced by the positive control, *E. coli* LPS. Similar increases in cytokine expression were observed when the vaccine proteins and OMVs were co-cultured, implicating the OMVs as the major cause.

There were no significant effects of any vaccine components on activity of activated protein C, platelet activation and platelet-leukocyte aggregation *in vitro*.

Reproductive and developmental toxicity

Fertility, early embryonic development, and pre- and post-natal development, including maternal function, were assessed in reproductive and developmental toxicity studies in female rabbits. Bexsero vaccine was administered at the clinical or higher dose levels. Female rabbits were administered 5 doses of rMenB protein antigens in the presence or

absence of OMV/NZ, with 3 doses administered IM pre-mating and 2 administered IM during gestation.

In the pilot study with up to double the human dose of Bexsero administered, the results suggested no overt hazard of vaccination to maternal animals or their developing fetuses through to gestation day (GD) 29. Similarly, the administration of rMenB proteins without OMV/NZ (up to double the clinical dose) had no toxic effects to maternal animals or their fetuses. Immunogenicity of all of the tested vaccine formulations was demonstrated in maternal animals by antibody titres to the antigen components of the vaccine and SBA titres to serogroup B strains of *N. meningitidis*, with antibodies also detected in pooled fetal sera.

In the pivotal study 5 consecutive IM doses of the Bexsero clinical dose were administered to female rabbits assigned to either Caesarean section at GD 29 or natural delivery, and assessment was at lactation day 29. There were no overt hazards identified due to vaccination in maternal animals, developing fetuses or offspring. An immune response was elicited in maternal animals with serum antibodies and SBA titres detected in fetuses and offspring 4 weeks after birth. Bexsero formulation was immunogenic in rabbits and was not a female reproductive or developmental toxicant in this study.

Three supportive reproductive and developmental toxicity studies conducted in rabbits were also submitted, investigating the effects of different rMenB formulations. A MenB NZ OMV vaccine with no recombinant proteins, licensed in New Zealand, was tested in study UBA00002.

There are some published reports of teratogenicity of LPS in animals. Significant increases in the numbers of fetuses with external abnormalities were observed in mice given a single SC injection of 0.5 µg/g body weight of *E. coli* LPS on GD 8 and examined on GD 18 (Carey *et al.*, 2003[15]). Hamsters given a single intravenous (IV) dose of LPS 0.1, 025, 0.5, 0.75, 5 or 25 µg/100 g body weight showed significant increases in fetal abnormalities at 0.25 µg/100 g body weight and above (Lanning *et al*, 1983[16]), with a no observed effect level (NOEL) of 0.1 µg/100 g body weight. However, the doses of LPS in mice and hamsters greatly exceed the potential maximum amount of LPS in Bexsero in a 50 kg woman. There was no evidence of teratogenicity in the reproductive and developmental study in which rabbits weighing 2.7-4.1 kg were administered the full human dose of Bexsero vaccine, containing 849 IU/mL endotoxin (batch X38D27N1).

Overall, the studies of Bexsero vaccine formulation and its investigated components raised no reproductive and developmental toxicological concerns in studies in female rabbits. The proposed Australian pregnancy category of B1[17] is acceptable.

Residuals

Potential vaccine residuals are endogenous compounds (DNA, host cell proteins, endotoxin) and exogenous residual chemicals. Endotoxin is also an essential component of the OMVs and is assessed in the *Toxicity* section above.

For other residual chemicals, the sponsor provided a literature-based toxicological risk assessment. Although there were limitations in the toxicological data for the residuals, appropriate safety factors to account for differences in species, dose route and uncertainty

[15] Carey LC *et al.*. Zinc treatment prevents lipopolysaccharide-induced teratogenicity in mice. *Birth Defects Research Part A*: 2003. Published online in Wiley InterScience (www.interscience.wiley.com).
[16] Lanning C *et al.* Teratogenic effects of endotoxin on the golden hamster. *Teratog. Carcinogen. Mutagen* 2003:3(2): 145-149.
[17] Use in pregnancy Category B1 is defined as: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

were applied. The data limitations are not considered critical in view of the large estimated safety multiples and the limited use of the vaccine (maximum of 4 doses with at least 1 month between doses).

Paediatric use

Bexsero is proposed for use in infants as young as 2 months of age. No toxicity studies were conducted in infant animals, however the immunogenicity studies in juvenile baboons (study 283886-01) and infant rhesus macaques (283887-01) included complete blood counts at each of the 3 sample times, with no adverse findings. In the pivotal toxicity study the full clinical dose was administered to rabbits weighing 4 kg, which is about 1.25-2.5 times the dose (on a bodyweight basis) in a 5-10 kg human infant.

Nonclinical summary and conclusions

- The immunogenicity of the proposed vaccine individual antigens and the clinical formulation (Bexsero) was assessed in mice, guinea pigs, rabbits, juvenile baboons and infant rhesus macaques. Bexsero was immunogenic in all test species, in terms of serum antibody (ELISA) and/or SBA titres. Passive protection of infant rats against bacteraemia by serogroup B strains was reported for mouse or guinea pig antisera to the vaccine antigens. Active protection was not tested due to the lack of animal models of infection with *N. meningitidis*, a human-specific pathogen.
- No dedicated safety pharmacology studies were submitted. Some safety pharmacology parameters were investigated in the toxicity studies.
- GLP-compliant single and repeat-dose toxicity studies in rabbits tested the clinical formulation (Bexsero) and related vaccines in rabbits. In the pivotal study, rabbits were injected IM with 5 consecutive doses of the clinical dose of Bexsero, or twice the clinical dose of antigens and the clinical dose of OMV-NW. In some studies, small, significant elevations in fibrinogen, globulin, and leukocyte and neutrophil counts were observed, consistent with an inflammatory/immune response to the vaccine. There was no evidence of systemic toxicity. Injection site reactions, characteristic of an aluminium-adjuvanted vaccine, were slightly more frequent or severe in vaccine-treated rabbits compared to controls, but were within acceptable levels and partially resolved within 14 days. The vaccine protein antigens, with or without OMVs, were immunogenic in rabbits.
- The vaccine contains a relatively large amount of LPS. Its bioavailability is substantially reduced by association with proteins in the OMVs and adsorption to $Al(OH)_3$. However, a toxicity study with a related OMV vaccine reported transient elevations in rectal temperature in rabbits, indicative of residual pyrogenicity.
- A range of *in vitro* studies investigated potential effects of the vaccine proteins and OMVs that might be related to the pathogenicity of *N. meningitidis*. The protein antigens alone or combined with OMVs and $Al(OH)_3$ were not cytotoxic to primary HUVECs, although some binding occurred at high concentrations. The vaccine protein antigens did not affect cell monolayer permeability, PT and aPTT in human plasma, nor activated protein C activity, platelet activation or platelet-leukocyte aggregation. The protein antigens induced some cytokines in HUVECs and human whole blood, however the increases were similar to those induced by some of the other registered vaccines. Outer membrane vesicles substantially increased levels of the pro-inflammatory cytokines IL-1, IL-6, TNF-α, IL-8 and IFN-γ in human whole blood *in vitro*.

- Reproductive and developmental toxicity studies in female rabbits injected with the clinical dose of Bexsero or related vaccines showed no overt hazard of vaccination to maternal animals, fetuses or 4 week old pups. Vaccine-specific antibodies were detected by ELISA and SBA in dams, fetuses and 4-week old offspring.

Conclusions and recommendation

- Vaccine immunogenicity was shown in terms of serum antibody and/or SBA titres in mice, guinea pigs, rabbits and non-human primates at doses one quarter to double the clinical dose in humans. Passive protection against bacteraemia was shown in infant rats administered antisera from vaccinated mice or guinea pigs. Active protection was not investigated due to the lack of animal models of infection with *N. meningitidis*, a human-specific pathogen.
- No dedicated safety pharmacology studies were conducted but some safety pharmacology parameters were investigated in the toxicity studies.
- GLP-compliant acute and repeat-dose toxicity studies with the clinical and related vaccine formulations showed small, significant increases in fibrinogen and globulin levels and in leukocyte and neutrophil counts, indicative of a transient immune/inflammatory response, but no systemic toxicity. Injection site reactions were slightly more frequent and severe in vaccinated rabbits in comparison with controls, but were within acceptable levels. The clinical dose of Bexsero (0.5 mL) administered in 2.3-3.8 kg rabbits was 1.3-2.1 times the dose proposed for a 5 kg infant, on the basis of bodyweight.
- The vaccine contains a relative large amount of LPS. LPS is highly pyrogenic in its free form but its pyrogenicity is substantially reduced when associated with proteins in OMVs, and is further reduced by adsorption of the OMVs to $Al(OH)_3$ adjuvant. However, a toxicity study with a related OMV vaccine reported elevated rectal temperatures in rabbits, indicative of residual pyrogenicity. Registration should be subject to satisfactory clinical investigation of vaccine pyrogenic potential, particularly in infants.
- GLP-compliant reproduction and developmental toxicity studies in which female rabbits were administered the clinical dose of Bexsero indicated no significant toxicity to dams, fetuses or pups. The proposed use in pregnancy Category B1 is considered appropriate.

The nonclinical evaluator raised no objections to the registration of Bexsero. Revisions were recommended to the nonclinical statements in the draft PI; details of these are beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The development of this meningococcal group B vaccine is based on two main areas of information relevant to meningococcal disease:

1. The epidemiology of meningococcal disease;
2. The chronology of development of previous meningococcal B vaccines used in response to epidemics in various countries then developed further with knowledge gained from identification of the genomic structure of the outer membrane proteins of serogroup B.

Invasive meningococcal disease occurs worldwide. Incidence varies in different regions of the world. Infants, children, and adolescents are the most vulnerable to developing invasive disease.

Symptoms of the disease occur rapidly and often result in severe outcomes. Despite the availability of medical treatment and effective antibiotics, 8-9% of IMD patients in developed countries die, increasing with age[18], and up to 11-19% of survivors have lifelong sequelae.[19] Each year approximately 1.2 million cases of IMD are recorded worldwide, of which 7,000 occur in Europe.[20] The overall incidence in European countries ranges from approximately 1-4 cases per 100,000 population. However, during epidemics this may increase to 800 cases or more per 100,000 population.

Over 90% of meningococcal meningitis and septicaemia is caused by five of the 13 meningococcal serogroups, that is, serogroups A, B, C, W-135 and Y.[21] The introduction of the conjugate serogroup C meningococcal vaccine changed the epidemiology of the disease in developed countries dramatically, leaving serogroup B as the predominant cause of disease. It is thought that the development of vaccines for prevention of serogroup B disease in industrialised nations and serogroup A conjugate vaccines for Africa could lead to global control of meningococcal disease.[22]

Serogroup B accounts for a high proportion of meningococcal disease cases in the Americas, Japan, Europe, Australia (> 80%) and New Zealand (87%). The global incidence of serogroup B has been estimated between 20,000 and 80,000 cases per year, accounting for 2,000-8,000 deaths annually.

Further details on the epidemiology of meningococcal disease are found in the CER (see Attachment 2of this AusPAR).

Vaccine clinical development program

To date, no broadly effective serogroup B meningococcal vaccines are available. Capsular polysaccharide vaccines have been used for the other meningococcal serogroups but the capsular polysaccharide of meningococcal serogroup B is poorly immunogenic in humans. This prompted research to focus on proteins in the outer membrane of meningococci as potential antigens for candidate vaccines. Serogroup B vaccines based on protein-containing OMV have been safe and effective in controlling epidemic disease caused by strains homologous 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.

This serogroup B meningococcal vaccine (Bexsero, also called rMenB+OMV NZ) was developed based on knowledge gained during vaccine development for the Norwegian (MenBvac vaccine) and New Zealand (MeNZB vaccine) epidemics, in conjunction with the

[18] European Centre for Disease Prevention and Control surveillance report for 2007 (ECDC, 2010).
[19] Kirsch EA, Barton RP, Kitchen L, and Giroir BP. Phathophysiology, treatment and outcome of meningococcemia: a review and recent experience. *Pediatr Infect Dis J*, 1996; 15:967-79
[20] World Health Organization (WHO), 2001
[21] Girard MP, Preziosi M, Aguado M, and Kieny MP *et al*. A review of vaccine research and development: Meningococcal disease. *Vaccine*, 2006: 24:4692–4700
[22] Khatami A and Pollard AJ. The epidemiology of meningococcal disease and the impact of vaccines. *Expert Rev. Vaccines*, 2010: 9(3);285–298.

identification of the *N. meningitidis* serogroup B genome sequence. The availability of the bacterial genome sequence allowed identification of conserved surface-exposed outer membrane proteins of serogroup B strains that were targets for bactericidal antibodies.[23]

Guidance

The process for the selection of the final formulation, dose and timing of vaccinations conformed to the Committee for Medicinal Products for Human Use (CHMP) *Guideline on clinical evaluation of new vaccines* (EMEA/CHMP/VWP/164653/2005).[24]

Contents of the clinical dossier

Scope of the clinical dossier

The clinical studies providing data for this submission are summarised in Table 4.

The submission contained the following clinical information:

Module 5:

This contains data from three Phase I clinical efficacy studies used in the development of the vaccine with an earlier formulation and a number of studies using the final vaccine formulation. Studies using the final formulation included 1 Phase I and 5 Phase II immunogenicity and safety studies in varying age groups, 1 Phase III immunogenicity and safety study in 11-17 year old population, and 1 Phase III immunogenicity, lot consistency and safety study in infants, with a separate report for booster dose after 12 months.

Module 2:

The sponsor's clinical overview, summary of clinical efficacy, summary of clinical safety, and literature references were provided.

The Bexsero Day 121 – Response to Clinical Questions raised by the European Medicines Agency (EMA; Day 120 questions) was also provided.

[23] Pizza M, Scarlato V, Masignani V, Giuliani MM *et al*. Identification of vaccine candidates against serogroup B meningococcus by whole-genome sequencing. *Science* 2000: 287:1816–1820.
[24] <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003870.pdf> Accessed 22/2/12.

Table 4. Overview of Clinical Studies for Australian Application

Study No	Population (Age at Enrollment), Schedule	Type of Study	Country	Vaccine Groups	N enrolled
V72P4	Adults (18-50 y) 0,2,6 months	Phase 2, Multi-Center Open	Italy Germany	**rMenB+OMV NZ** + MenACWY at 6 months	54
V72P5	Adults (18-40 y) 0,1,2 months	Phase 1, Observer blind, Single-center, Randomized	Switzerland	**rMenB+OMV NZ**	28
				rMenB+OMV NW	28
				rMenB	14
V72P6	Infants (2 months) 2,4,6 12, or 12 months	Phase 2, Open label Multicenter Randomized Controlled	UK	rMenB (2,4,6 and 12 months)	48
				rMenB+OMV NZ (2,4,6 and 12 months)	50
				rMenB (12 months only)	25
				rMenB+OMV NZ (12 months only)	24
V72P9	Infants (6-8 months) 0, 2 plus dose at 12 months of age)	Phase 2 Single blind Single center Randomised	UK	rMenB	30
				rMenB+OMV NZ	30
V72P10	Adolescents (11-17 y) 1,2 or 3 doses at 0, 1, 2 months	Phase 2b/3 Observer-blind, Multi-center, Randomized Controlled	Chile	**rMenB+OMV NZ** at month 0, Placebo at month 1 Placebo at month 2	375
				rMenB+OMV NZ at month 0, **rMenB+OMV NZ** at month 1 Placebo at month 2	375
				rMenB+OMV NZ at month 0, Placebo at month 1 **rMenB+OMV NZ** at month 2	380
				rMenB+OMV NZ at month 0, **rMenB+OMV NZ** at month 1 **rMenB+OMV NZ** at month 2	373
				Placebo at month 0, Placebo at month 1 Placebo at month 2	128

Table 4 continued. Overview of Clinical Studies for Australian Application

Study No	Population (Age at Enrollment), Schedule	Type of Study	Country	Vaccine Groups	N enrolled
V72P12	Infants: (2 months) 2,3,4 months, Or 2,4,6 Months,	Phase 2b Open Label, Parallel-group Multi-center Randomized	UK Belgium Germany Czech Rep Italy Spain	**rMenB+OMV NZ** at 2,4,6 months, concomitant routine vaccinations[a]	627
				rMenB+OMV NZ at 2,4,6 months, routine vaccinations at 3,5,7 months	628
				rMenB+OMV NZ at 2,3,4 months, concomitant routine vacinations	318
				Routine vaccinations only at 2,3, 4 months	312
V72P13	Infants (2 months) 2,4,6 months w/6-months f/u	Phase 3 Partially blinded, Multi-Center Randomized Controlled	Italy Germany Austria Czech Rp Finland	**rMenB+OMV NZ** (lot 1) +routine vaccinations	833
				rMenB+OMV NZ (lot2) +routine vaccinations	828
				rMenB+OMV NZ (lot3) +routine vaccinations	820
				Routine vaccinations	659
				MenC+routine vaccinations	490
V72P13 E1	Infants (12 months) Booster (or 2 doses for naive controls)	Phase 3 Open label Multi-Center Extension Study of V72P13	Italy Germany Austria Czech Rp Finland	**rMenB+OMV NZ**+routine (in V72P13 open label subset)/ **rMenB+OMV NZ** and MMRV at 12 months (in V72P13E1)	629
				rMenB+OMV NZ+routine (in V72P13 open label subset)/ **rMenB+OMV NZ** at 12mo, MMRV at 13mo (in V72P13E1)	633
				Routine (in V72P13 open label subset)/MMRV at 12mo, **rMenB+OMV NZ** at 13 and 15 mo (in V72P13E1)	285
				Routine (in V2P13 open label subset)/ **rMenB+OMV NZ** and MMRV at 12mo, **rMenB+OMV NZ** at 14mo (in V72P13E1)	117
				rMenB+OMV NZ + Routine (in V2P13 observer blind subset)/	137

Table 4 continued. Overview of Clinical Studies for Australian Application

Study No	Population (Age at Enrollment), Schedule	Type of Study	Country	Vaccine Groups	N enrolled
				rMenB+OMV NZ and MMRV at 12 months (in V72P13E1)	
				rMenB+OMV NZ + Routine (in V2P13 observer blind subset)/ **rMenB+OMV NZ** at 12mo, MMRV at 13mo (in V72P13E1)	156
				MenC+routine (in V72P13 observer blind subset)/ **rMenB+OMV NZ** and MMRV at 12months (in V72P13E1)	152
				MenC+routine (in V72P13 observer blind subset)/ **rMenB+OMV NZ** at 12mo, MMRV at 13mo (in V72P13E1)	140
V72P13 E2	Infants (24-27 months Persistence after booster, 12 months Persistence after 2 doses and booster dose)	Phase 3 Open label Multi-Center Extension Study of V72P13E1	Czech Rp Finland	**rMenB+OMV NZ**+routine (in V72P13)/ **rMenB+OMV NZ** and MMRV at 12 months (in V72P13E1)	152
				rMenB+OMV NZ+routine (in V72P13)/ **rMenB+OMV NZ** at 12mo, MMRV at 13mo (in V72P13E1)	154
				Routine (in V72P13)/ MMRV at 12mo, **rMenB+OMV NZ** at 13 and 15 mo (in V72P13E1)	67
				Routine (in V2P13 open label subset)/ **rMenB+OMV NZ** and MMRV at 12mo, **rMenB+OMV NZ** at 14mo (in V72P13E1)	19
				New naive subjects, 23-27 months of age, **rMenB+OMV NZ** at 24mo and 26 mo	116

[a] Routine vaccinations: Infanrix Hexa (DTPa-HBV-IPV/Hib) and Prevenar (PCV7)

Paediatric data

The submission included efficacy (immunogenicity) and safety data in children. Four of the Phase II studies were in children (from 2 months of age). There were 3 Phase III studies in children, a Phase II study in adolescents as well as a Phase IIb/III study in adolescents.

Good clinical practice

As far as can be verified (and stated explicitly in the submission) all studies complied with good clinical practice (GCP). All studies were performed according to the ethical principles

of the Declaration of Helsinki and in compliance with GCP and the applicable regulatory requirements for the country in which they were conducted.

Pharmacokinetics

Pharmacokinetic studies are generally not performed for injectable vaccines and kinetic properties of vaccines do not provide information useful for establishing adequate dosing recommendations (see Guideline EMEA/CHMP/VWP/164653/2005).

Pharmacodynamics

Studies providing pharmacodynamic data

Study V72P5 was the first to evaluate safety and immunogenicity of the final vaccine formulation containing the three recombinant proteins with OMV purified from *N. meningitidis* serogroup B New Zealand strain NZ98/254 (that is, Bexsero or rMenB+OMV NZ). Healthy adults 18 to 40 years of age received 3 doses of either rMenB+OMV NZ, rMenB OMV NW or rMenB according to a 0, 1, 2-month schedule. Although all three vaccines were immunogenic with similar safety profiles, the immune response against hypervirulent ST-41/44 complex/lineage III strains was higher in the rMenB+OMV NZ group.

Two Phase II studies performed in the UK explored the safety and immunogenicity of rMenB with or without OMV NZ in infants: one (Study V72P6) when administered to healthy infants at 2, 4 and 6 months of age, followed by a booster at 12 months of age; and the other (Study V72P9) when administered to healthy infants aged 6-8 months at enrolment time, with 2 doses separated by 2 months, followed by a booster at 12 months of age.

This formulation was selected for further clinical development based on: 1) evidence of enhanced coverage against the hypervirulent ST-41/44 complex/lineage III strains; 2) the experience in the infant population with Novartis' NZ98/254 OMV-based vaccine, MeNZB, which was shown to be safe and efficacious in the control of the epidemic in New Zealand.

The pivotal Phase III Study V72P13 and its extension Study V72P13E1 examined the safety and immunogenicity of rMenB+OMV NZ when administered to infants at 2, 4 and 6 months of age with a booster vaccination at 12 months alongside currently recommended routine vaccinations. This study was conducted in a large population of infants from 5 European countries.

V72P12, a Phase IIb study conducted in infants 2 months of age on enrolment, was performed in 6 European countries. This study evaluated two differing schedules for rMenB+OMV NZ (a 2, 4, 6- or 2, 3, 4-month schedule) with concomitant or intercalated routine vaccination and showed that antibody responses to rMenB+OMV NZ were similar regardless of the schedule.

V72P10**,** a Phase IIb/III study of 1, 2 or 3 rMenB+OMV NZ vaccinations in 11-17 year old adolescents in Chile, was performed in order to evaluate safety and immunogenicity of the vaccines in adolescents and select the proper vaccination schedule.

Mechanism of action and measures of efficacy

The mechanism of action of this vaccine is the induction of protective antibodies. Although the best evidence for its efficacy would be epidemiological data, the standard surrogate marker for the efficacy of vaccines is the induction of specifically related antibodies. So, in terms of measuring immunogenicity, the production of SBA against the meningococcal B antigens included in this vaccine is used as the correlate of protection.

The selection of the SBA using human complement as the main method for assessing immunogenicity was based on generally accepted scientific methods for assessment of human immunity to the meningococcus.[25] The SBA measures the level of antibodies that recognise bacterial surface antigens and are capable of directing complement-mediated bacterial lysis, the main mechanism by which *N. meningitidis* serogroup B strains are killed after natural infection.

Evaluator's overall conclusions on pharmacodynamics

The selection of antigens, dose and vaccine composition is based on both clinical experience and data collected prior to the studies included in this application. The studies described briefly above are discussed more fully in the section on *Efficacy*. In this section, they are discussed in relation to the choice of vaccination schedules.

As well as showing efficacy in all studies, the studies in infants under 6 months had best results after 3 vaccinations. There was no effect on efficacy when the schedule was 2, 3, 4 months or 2, 4, 6 months and also when the vaccine was given separately or concomitantly with other childhood vaccines. This data is very helpful in that it provides flexibility in terms of recommendations. The easiest way to administer this vaccine will probably be concomitantly with other vaccines. The responses waned over 6 months and then greatly benefited from a booster at 12 months. The studies in infants over 6 months show that a 2-dose regimen (2 months apart) is sufficient, with little benefit from a third primary dose, although there was benefit from a booster in the second year of life. In the older groups (11 years and on), 2 doses (2 months apart) were sufficient (and better than 1 dose) and there was no added benefit from a third dose. In adolescents, it did not matter whether these 2 vaccinations were given 1 month apart, 2 months apart or 6 months apart. It is important to note that there is no data in children 2-10 years (but a clinical study in this age group is planned[26]).

Efficacy

Dosage selection for the pivotal studies

Both the pivotal and other efficacy studies were involved in determining the optimal schedule selection. The studies used in the development program leading up to the selection of schedules for the pivotal studies are briefly described here.

Clinical Study V72P4

This was a Phase II, open-label, multi-centre study in healthy at-risk adults (18 to 50 years of age) routinely exposed to *N. meningitidis*, designed to explore the immunogenicity and safety of 3 doses of rMenB+OMV NZ given at 0, 2 and 6 months (and to explore the immunogenicity of a single dose of Novartis MenACWY conjugate vaccine given at 6 months concomitantly with the third rMenB+OMV NZ vaccination). rMenB+OMV NZ effectively induced bactericidal antibodies in adults following 2 doses at 0 and 2 months as measured by a human serum bactericidal assay (hSBA) using human complement against the three reference strains 44/76, 5/99 and NZ98/254. A third dose at 6 months did not produce any further benefit.

Clinical Study V72P5

This Phase I study was designed to obtain preliminary data in healthy adults (18 to 40 years of age, N=70) on the similarity of the safety profiles and the similarity of the humoral

[25] Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. *J. Exp. Med* 1969:129(6):1307–26.
[26] Sponsor comment: as of October 2013, this study is on-going

immune responses, as measured by hSBA and ELISA, of the addition of the Norwegian or the New Zealand OMVs to the Novartis meningococcal B recombinant vaccine. In the rMenB+OMV NZ group and the rMenB+OMV NW group, the proportion of subjects with hSBA ≥ 1:4 increased from baseline to 1 month after the third vaccination for 14 of the 15 tested *N. meningitidis* serogroup B strains; in the rMenB group, this was the case for 13 of the strains. Against strains 44/76, and 5/99 all (100%) subjects in all vaccine groups had achieved hSBA ≥ 1:4 at 1 month after the second vaccination. Against strain NZ98/254, 96% of the subjects in the rMenB+OMV NZ group achieved hSBA ≥1:4 against at 1 month after the second dose while this percentage was lower in the rMenB+OMV NW group (74%) and in the MenB group (69%). These results encouraged the further development of the rMenB+OMV NZ strain.

Clinical Study V72P6

This was a Phase II, open label, multi-centre, controlled, randomised study, the first to be conducted in healthy infants aged 2 months at time of enrolment. Subjects received rMenB or rMenB+OMV NZ vaccinations IM according to a 2, 4, 6 and 12 months of age immunisation schedule or as a single dose at 12 months of age. The immunogenicity results demonstrated that rMenB+OMV NZ could effectively induce bactericidal antibodies in infants following 3 doses at 2, 4 and 6 months of age, as measured by hSBA against the three MenB strains 44/76, 5/99 and NZ98/254. Bactericidal antibody was also found to persist against the three vaccine antigens at 12 months of age, 6 months after the primary series, but the percentages of subjects with hSBA ≥1:4 had fallen from 87% at 1 month after the third vaccination to 68% at 12 months of age for strain 44/76, from 95% to 88% for strain 5/99, and from 85% to 36% for strain NZ98/254, demonstrating the need for a booster dose. The responses could be further boosted with a 4th dose of rMenB+OMV NZ at 12 months of age, demonstrating that the infants had been primed with the 3 doses and immunological memory had been generated. The control subjects in this study who received a single dose of rMenB+OMV NZ vaccine at 12 months of age served as comparators for the 12-month booster response in the subjects receiving the vaccine at 2, 4 and 6 months. The proportion of subjects achieving hSBA ≥1:4 against the three reference strains was consistently lower for the control subjects receiving a single dose at 12 months of age as compared to the fourth dose response in the rMenB+OMV NZ subjects group at the same age (73% versus 100% for strain 44/76, 73% versus 97% for strain 5/99, and 18% versus 94% for strain NZ98/254). This study suggested that a 3 dose primary course was required in 2-month-old infants, a booster dose was required after the primary course, and that 1 vaccination was insufficient in naïve infants of 12 months of age and above. The study provided sufficient evidence to warrant the further development and evaluation of the rMenB+OMV NZ vaccine in phase 3.

Studies providing efficacy data

There are nine studies included in this application to support the immunogenicity of the vaccine: 3 studies (V72P10, V72P4, and V72P5) in subjects 11 years of age and older (adolescents 11 to 17 years of age and adults 18 to 50 years of age) and 6 studies (V72P13, V72P13E1, V72P13E2, V72P12, V72P9, and V72P6) in the infant and toddler/children populations. Data are available for 1622 vaccinated (of 1631 enrolled) adolescent subjects 11 to 17 years of age, 81 adult subjects 18 to 50 years of age, and 4843 infant subjects 2 to 23 months of age exposed to at least 1 dose of the rMenB+OMV NZ vaccine.

Studies in adolescents and adults

- V72P10 was a pivotal Phase IIb/III study in this age group assessing various vaccination schedules conducted in Chile in 1631 adolescents 11 to 17 years of age.

- V72P4 was a Phase II, open-label study conducted in Italy and Germany on 53 vaccinated laboratory workers aged 18 to 50 years who were routinely exposed to *N. meningitides.*
- V72P5 was a Phase I study conducted in Switzerland in 70 adults 18 to 40 years of age.

Studies in Infants

- V72P13 was a pivotal, Phase III, lot comparison and non-interference study conducted in Italy, Germany, Austria, Finland and the Czech Republic in 3630 infants aged 2 months at entry.
- V72P13E1 was the extension study to the above, investigating booster response and non-interference with routine measles, mumps, rubella and varicella live-vaccine (MMRV) vaccination in 2249 toddlers in their second year of life.
- V72P13E2 was an extension study of V72P13E1 and enrolled 508 subjects, comprising 392 subjects who had participated in the open-label, immunogenicity subset conducted in Finland and the Czech Republic. The study investigated antibody persistence 1 year after the booster dose given in V72P13E1, and booster response in toddlers 1 year after a 2 dose schedule administered in the second year of life. An additional group of 116 naïve subjects (defined as subjects who had never previously received any meningococcal B vaccine) approximately 24 months of age were recruited at the same study sites.
- V72P12 was a Phase IIb study comparing different vaccination schedules and non-interference with routine vaccinations, conducted in the UK, Spain, Italy, Belgium, Germany and Czech Republic, in 1885 infants aged 2 months at entry.
- V72P9 was a Phase II study conducted in the UK in 60 infants aged 6-8 months at entry.
- V72P6 was a Phase II study conducted in the UK in 147 infants aged 2 months at entry.

In all studies, responses in vaccine recipients were measured by a SBA using human complement (hSBA) as a correlate of clinical efficacy against serogroup B meningococcus. Serum was collected just before vaccination (Study Day 1), and at 30 days after the last vaccination in all studies. Serum was also collected 30 days after the second vaccination in Studies V72P5, V72P6 and V72P9, and 30 days after every vaccination in Studies V72P4 and V72P10. In Study V72P13E1, serum was also collected and analysed six months after the third vaccination in parent Study V72P13 to assess antibody persistence after the primary infant vaccination course.

Evaluator's conclusions on clinical efficacy for active immunisation against invasive disease caused by *N. meningitidis* of individuals from 2 months of age and older

The data included in this dossier is complex and expansive but appears to support the following:

- The immune responses to the rMenB+OMV NZ (Bexsero) vaccine are sufficient in infants who receive the first vaccination at 2 months of age after 3 doses given at least 1 month apart with or without routine vaccines administered concomitantly. It also appears that these vaccines can be given 1 month apart without any change in efficacy. The sufficiency of the immune responses to rMenB+OMV NZ when administered concomitantly with routine vaccines as a 3-dose infant primary series at 2, 4 and 6 months of age is supported by the data from V72P13 and V72P12 Studies. A non-inferiority approach was used to evaluate the immune responses to rMenB+OMV NZ when administered concomitantly with or without routine vaccines in Study V72P12, using predefined noninferiority criteria.

- The immune responses to the vaccine are sufficient in immunologically naïve older infants and toddlers 6 months of age and older after 2 doses of rMenB+OMV NZ given 2 months apart. The data from Study V72P9 in which a 2-dose schedule at 6 to 8 months of age was used, and in immunologically-naïve toddlers in Study V72P13E1 using a 2-dose schedule with or without concomitant vaccines, appear to support this.
- The immune responses to a booster dose given to toddlers in their second year of life induce a persistent booster response, either following a 3-dose infant primary schedule given 1 or 2 months apart starting at 2 months of age, or following a 2-dose older, immunologically-naïve infant schedule given 2 months apart starting at 6 months. Adequate immune responses to a booster dose given at 12 months of age with or without concomitant MMRV vaccination, following a 3-dose primary infant series, were shown in Study V72P13E1. The immune responses to a rMenB+OMV NZ dose at 12 months of age after a 2-dose primary series in naïve older infants in Study V72P9 was sufficient. Data from Study V72P13E2 showed a good response to a booster dose given at 1 year following a 2-dose catch-up series in toddlers in the second year of life.
- Immune responses were assessed 1 month following completion of the primary vaccination course in infants (Studies V72P12, V72P13), older infants (V72P9), adolescents (V72P10) and adults (V72P4 and V72P5). In the extension studies (V72P13E1 and V72P13E2) the durability of these responses in the infants/toddlers and the effect of booster doses were further studied. Persistence of bactericidal antibodies at 12 months of age (following vaccination at 2, 4 and 6 months) prior to the booster was evaluated in V72P13E1 (as well as 1 month post-booster). The persistence of antibodies 12 months after the 12-month booster (as well as 12 months after primary 2-dose toddler vaccination) was then evaluated in Study V72P13E2.
- Lot to lot consistency of the rMenB+OMV NZ was shown in Study V72P13.
- Concomitantly administered routine infant and toddler vaccinations elicit similar immune responses when given with rMenB+OMV NZ vaccine as compared to the same vaccines given alone. This is supported by the data from Study V72P12 and Study V72P13.
- The response to the first dose of the 2-dose series of the four antigens contained in Priorix-Tetra (measles, mumps, rubella and varicella) is non-inferior when given with or without rMenB+OMV NZ (Study V72P13E1), using predefined statistical criteria.
- The immune responses to the rMenB+OMV NZ vaccine are sufficient in adolescents 11-17 years of age after 2 doses given at least 1 month apart. This appears to be supported by the results of Study V72P10. All available data for subjects in this age group by schedule were combined to increase numbers analysed.
- The immune responses to the rMenB+OMV NZ vaccine appear to be sufficient in adults 18-50 years of age after 2 doses, given at least 1 month apart. This was supported by the results of Studies V72P5 and V72P4 (small studies).
- There is no specific data for efficacy in children aged 2-10 years of age.

Safety

Studies providing evaluable safety data

For all the studies discussed in the *Efficacy* section above, safety and tolerability were co-primary objectives (with immunogenicity). All subjects receiving at least 1 injection and providing post-baseline safety data were included in the safety and tolerability analyses.

The number of participants available for safety data in the different studies is summarised in Table 5 (primary vaccination) and Table 6 (booster vaccination).

Table 5. Overview of Clinical Studies Included to Support rMenB+OMV NZ Vaccine Safety of Infants (Primary Series) and Adolescents and Adults, 2 Months of Age and Older

Age groups Study Number (Phase)	Study Design	Age at enrollment	Schedule	Number in the Safety Population [a]		Concomitant Routine Vaccines
				rMenB+OMV NZ	Control	
Adolescents and Adults						
V72P4 (Phase 2)	Open-label, multi-center, safety, and immunogenicity study in healthy (at-risk) adults	18-50 years	0-2-6-month schedule with 2-months safety follow-up	53	None	None
V72P5 (Phase 1)	Observer blind, single-center, randomized, safety, and immunogenicity study in healthy adults	18-40 years	0-1-2-month schedule with 6-months safety follow-up	28	None	None
V72P10 (Phase 2b/3)	Observer-blind, multi-center, randomized, controlled, safety, and immunogenicity study in healthy adolescents with various schedules	11-17 years	0; 0-1; 0-2; 0-6; 0-1-2; 0-1-6; 0-2-6-month schedules with 6-months safety follow-up [b]	1631	None (Placebo)	None
Total				1712	None	
Infants and Toddlers						
V72P6 (Phase 2)	Open-label, multi-center, randomized, controlled, safety, and immunogenicity study in healthy infants with various schedules (including a booster dose)	2 months	2-4-6-month schedule with a booster dose at 12 months of age with 6-months safety follow-up	50	49 (Routine)	Pediacel, Prevenar
		12 months	1 dose at 12 months of age with 6-months safety follow-up	24	None	Menitorix
V72P9 (Phase 2)	Single-blind, single-center, randomized, safety, and immunogenicity in healthy infants (includes a booster dose)	6-8 months	6-8-month schedule with a booster dose at 12 months and includes a 6-months safety follow-up	30	None	None
V72P12 (Phase 2b)	Open-label, parallel-group, multi-center, randomized, safety, and immunogenicity in healthy infants with various schedules	2 months	2-4-6-and 2-3-4-month schedule with 6-months safety follow-up	1570	312 (Routine)	InfanrixHexa and Prevenar
V72P13 (Phase 3)	Partially-blinded, multi-center, randomized, controlled, safety, and immunogenicity, lot-to-lot consistency in healthy infants	2 months	2-4-6-month schedule with 6-months safety follow-up	2480	1149 (Routine or MenC conjugate with routine)	InfanrixHexa and Prevenar
V72P13E1 (Phase 3)	Open-label, multi-center, extension study of V72P13	12 months	1 dose in vaccine naive toddlers 12 months of age for original control group in V72P13 with 6-months safety follow-up	291	None	Subset with Priorix-Tetra
		12-13 months	2 doses in vaccine naive toddlers 12 or 13 months of age for original control group in V72P13 with 6-months safety follow-up	401[c]	None	Subset with Priorix-Tetra
Total				4846	1510	

Table 6. Overview of Clinical Studies Included to Support rMenB+OMV NZ Safety (Booster Vaccination)

Study Number (Phase)	Study Design	Age at enrollment	Schedule	Number in the Safety Population		Concomitant Routine Vaccines
				rMenB+OMV NZ	Control	
V72P6 (Phase 2)	Open-label, multi-center, randomized, controlled, safety, and immunogenicity study in healthy infants with various schedules (including a booster dose)	12 months	Booster at 12 months of age with 6-months safety follow-up	48[d]	None	Menitorix
V72P9 (Phase 2)	Single-blind, single-center, randomized, safety, and immunogenicity in healthy infants (includes a booster dose)	12 months	Booster at 12 months of age with 6-months safety follow-up	27[b]	None	None
V72P13E1 (Phase 3)	Open-label, multi-center, extension study of V72P13	12 months	Booster at 12 months of age with 6-months safety follow-up	1555	None	Priorix-Tetra
V72P13E2 (Phase 3)	Open-label, multi-center, extension study of V72P13E1	24 months	Booster dose given one year after 2 doses given to vaccine naive toddlers in V72P13E1 – 30 day safety data	85	None	None
Total				1715	0	

Patient exposure

The total number of subjects exposed to at least 1 dose of the rMenB+OMV NZ vaccine was 6555 subjects (from 2 months of age), including 4843 infants and toddlers, 1631 adolescents (11 to 17 years of age) and 81 adults (18 to 50 years of age). Of the subjects who received the primary infant series of rMenB+OMV NZ, 1630 received a booster dose

in the second year of life. Of the subjects who received the 2-dose catch-up schedule in the second year of life, 85 received a booster dose 12 months after the second dose.

Post-marketing experience

At the time, there was no post-marketing experience for rMenB+OMV NZ as the vaccine was not marketed yet. There was some information relevant to the OMV component of the rMenB+OMV NZ vaccine from the experience with OMV-based vaccines used worldwide for the control of local epidemics. It concurs with safety data from clinical trials with OMV vaccines MenBvac and MeNZB and also with surveillance data from the vaccination campaign. Fever is a characteristic feature of OMV vaccines when administered in the first year of life. The most directly relevant data comes from the New Zealand serogroup B outbreak, where a component of the rMenB+OMV NZ vaccine, as MeNZB, was used to control the clonal outbreak and was intensely studied in post-marketing safety analyses. The results, where self-limited mild to moderate fever was not accompanied by either increased rates of medical attention or increased rates of febrile seizures[27,28] are reassuring and will be important to validate in post-marketing studies of rMenB+OMV NZ. Kawasaki Disease[29] was also specifically studied and not found to be increased in frequency after implementation of MeNZB vaccination.[30]

Evaluator's overall conclusions on clinical safety

This vaccine has a very high incidence of local reactions at the injection site of rMenB+OMV NZ. These consisted of tenderness, erythema and induration. Overall, most of the local reactions were transient and resolved within the 7 day observation window. The majority of reactions were mild or moderate in nature. Other than for tenderness, severe local reactions were infrequent at the rMenB+OMV NZ injection site. In infants and toddlers, a slightly lower percentage of subjects reported solicited local reactions at the injection site of rMenB+OMV NZ when it was given alone at 2, 4 and 6 months (routine vaccines at 3, 5 and 7 months) than when it was administered concomitantly with the routine vaccines, whether at the 2, 3 and 4 month or 2, 4, 6-month schedules. rMenB+OMV NZ elicited higher local reactions rates compared with MenC vaccine and the routine vaccines Infanrix Hexa and Prevenar. Local reaction rates for rMenB+OMV NZ were common in all age groups studied and did not vary much according to the number of the vaccination in the schedule.

Solicited systemic reactions were common in infants and toddlers following vaccination with rMenB+OMV NZ. Percentages for solicited systemic reactions were higher (apart from rash) in infants administered rMenB+OMV NZ concomitantly with routine vaccines at the 2, 4, 6-month schedule (up to 86%) compared to those subjects receiving MenC vaccine with routine vaccines or routine vaccines alone. Most of the systemic reactions occurred within the first 3 days and were transient with few continuing past the day 7

[27] Holst J, Feiring B, Fuglesand J. E, Hoiby E.A, Nokleby H, Aaberge I.S, Rosenqvist E. Serum bactericidal correlates with the vaccine efficacy of outer membrane vesicle vaccines against *Neisseria meningitidis* serogroup B disease. *Vaccine* 2003:21:734-737.
[28] Stehr-Greena P, Radkea S, Kieft C, Gallowaya Y, McNicholas A, and Reid S. The risk of simple febrile seizures after immunisation with a new group B meningococcal vaccine, New Zealand. *Vaccine* 2008:26:739-742.
[29] Kawasaki Disease is a rare syndrome of unknown origin. In the clinical studies, a "confirmed" case of KD was defined by the Expert Panel as one that met the classical case definition of KD: fever of >5 days duration and the presence of at least 4 of the 5 other principal clinical signs (rash, cervical lymphadenopathy, bilateral conjunctiva infection, oral mucosal changes and peripheral extremity changes). Patients whose illness did not meet the KD case definition but who had coronary artery abnormalities consistent with KD were also classified as a confirmed case.
[30] McNicholas A, GallowayY, Stehr-Green P, Reid S, Radke S, Sexton K, Kieft C, Macdonald C, Neutze J, Drake R, Isaac D, O'Donnell M, Tatley M, Oster P, and O'Hallahan J. Post-Marketing Safety Monitoring of a New Group B Meningococcal Vaccine in New Zealand, 2004–2006. *Human Vaccines* 2007:3:5, 196-204.

observation window. The majority of reactions were mild or moderate in nature. As for the local reactions, there was no apparent cumulative effect of the booster dose of rMenB+OMV NZ. Of note, in infants, the highest rate of fever after rMenB+OMV NZ was observed at 6 h post-vaccination (Day 1) and its duration was transient, resolving for most of the subjects by 48 h after vaccination on Day 3.

This very high incidence of fever has implications both for medical practitioner recommendations in terms of infant vaccination scheduling and patient (or parent) acceptance. Options to lower the incidence of fever include the prophylactic use of antipyretics (being examined in Study V72P16 which is ongoing but looks to be effective according to a preliminary report) or by alternating the administration of rMenB+OMV NZ and other routine childhood vaccinations. It will be important that the incidence of fever is explicitly discussed by medical practitioners with patients (parents) prior to administration. It also has implications for the incidence of febrile convulsions, given the age group at risk for these. In infants with a history of febrile convulsions, it may be worth taking special measures to lower the risk of fever (separation from other vaccines and the use of antipyretics).

As well as fever, there are a number of other adverse events of significance reported in the infant studies. These are Kawasaki Disease, hypotonic-hyporesponsive episodes, and both febrile and non-febrile seizures. The few Kawasaki Disease cases that occurred in the rMenB+OMV NZ clinical studies do not allow a definitive assessment of the causal relationship between rMenB+OMV NZ vaccination and Kawasaki Disease. Furthermore, the co-administration of rMenB+OMV NZ with other vaccines is a confounding factor in many of the cases. Similar considerations apply for the other adverse event of interest. Although these may not be causally related to the vaccine (or even occur in a higher than normal incidence in the studies) they warrant further attention in the post-marketing studies.

First round benefit-risk assessment

Assessment of benefits

The benefits of rMenB+OMV NZ in the proposed usage are:

- This appears to be a vaccine that will provide broad coverage against the diverse strains of serogroup B *N. meningitidis*. The vaccine induces robust immune responses in individuals of all ages. In infants, a 3-dose regimen beginning at age 2 months induces a bactericidal antibody titer that correlates with protection against strains containing the vaccine antigens in 79-100% of vaccinees (assessed 1 month post-primary vaccination course). In older infants, toddlers, adolescents and adults, 2 doses of the vaccine given at 1 to 2 month intervals induces protective bactericidal antibody titres against the strains containing the vaccine antigens in nearly 100% of subjects. In toddlers, persistence of antibodies has been shown at 12 months post-vaccination.
- There is very limited data on functional immune response against NHBA given that a suitable reference strain for evaluating NHBA-specific bactericidal killing (strain M10713) was identified late in the development program and has only been used in a subset of participants in Study V72P13 and Study V72P13E1 (prior to this an ELISA test was used as a surrogate).
- It appears that this vaccine can be given either concurrently with or interspersed between other routine infant and toddler vaccines. The immune responses to antigens of the concomitantly administered vaccines were generally similar when given with rMenB+OMV NZ or alone.
- The proportion of subjects experiencing systemic reactions, unsolicited adverse events, and serious adverse events was generally similar across groups. For infants,

the rates of local and systemic reactions, including fever, were higher in the recipients of rMenB+OMV NZ when given concomitantly with routine vaccines as compared with recipients of routine vaccines alone. However, most of these events were categorised as mild or moderate, were transient, and did not lead to increased rates of health care utilisation or specific medical sequelae. Further, when the rMenB+OMV NZ vaccine was given separately from routine vaccines, the rates of local and systemic reactions appeared similar in both groups. These data support administration of rMenB+OMV NZ alone or concomitantly with routine paediatric vaccines.

Assessment of risks

The risks of rMenB+OMV NZ vaccine in the proposed usage are:

- There is a potential issue that it doesn't cover the circulating serotypes. Although there are some good data from the Meningococcal Antigen Typing System (MATS[31]) tests done by Novartis indicating that the vaccine will be effective against the majority of *N. meningitidis* serotypes, this was done on 172 isolates. It will be important to do ongoing laboratory and clinical data collection to assess the appropriateness of the vaccine to circulating serotypes.
- The vaccine has a high incidence of mild-moderate side effects, particularly in infants, although these were not judged to be serious and they resolved quickly. Local reactions such as pain and erythema were experienced by the majority of recipients. Fever and malaise were also very common, although these generally resolved quickly. There was a very high incidence of fever occurring the day after vaccination, particularly when rMenB+OMV NZ was co-administered with routine childhood vaccinations.
- The vaccine has a low incidence of significant adverse events but it will be important to continue to monitor these in order to be able to detect any causal relationship to Kawasaki Disease and seizures (not found in the data supplied in this application).

Assessment of benefit-risk balance

The benefit-risk balance of rMenB+OMV NZ vaccine, given the proposed usage, is favourable.

Invasive meningococcal disease can be a severe illness associated with a high case-fatality rate and a high percentage of survivors suffering from permanent neurologic and other sequelae. In Australia the proportion of meningococcal disease cases caused by serogroup B is relatively high, accounting for approximately 80% of all cases. However, unlike serogroups A, C, W, and Y, there is currently no effective vaccine that protects against serogroup B meningococcal disease. The disease most commonly affects infants below 1 year of age.

The rMenB+OMV NZ vaccine has been developed based on proven efficacy of OMV-based vaccines and on the use of antigens which are conserved and appears to be highly effective in inducing bactericidal antibodies in humans beginning from 2 months of age. These studies have shown a high level of efficacy at 1 month following the primary course of vaccination. There is also data showing persistence of antibodies 12 months after the primary course in infants and toddlers. One caveat to this is the fact that NHBA-specific bactericidal killing was only directly assessed in a small subset of participants in Study V72P13/V72P13E1.

[31] MATS is a unique method for assessing whether a given strain is susceptible to killing by antibodies induced against the four major antigen components of the rMenB+OMV NZ vaccine. MATS was developed by Novartis as an indicator of the potential for coverage of circulating strains by the vaccine.

The high rate of mild-moderate local and systemic side effects, particularly the high rates of fever, when co-administered with routine childhood vaccinations was also raised as a concern by the European Medicines Agency (EMA) in the Agency's Day 120 questions. In the response to these questions, Novartis considers that the context and the benefit to be seen from using the vaccine far outweigh this problem and has stated the following: "*Fever associated with rMenB+OMV NZ vaccine given concomitantly with routine vaccinations is predictable, mild-to-moderate in severity, transient, and when properly communicated does not result in an increased frequency of medical evaluations."* This has merit, although the risks will need to be clearly articulated to recipients (or parents of recipients) prior to administration, with appropriate instruction about how to manage any outcomes.

Another option to reduce the possibility of post-vaccination fever is through the use of prophylactic antipyretics. The results of Study V72P16 show that prophylactic paracetamol reduced the percentage of subjects reporting fever after any dose (fever ≥ 38.0°C) was reduced from 88% down to 76%, and fever ≥ 38.5°C and ≥ 39.0°C was reduced from 69% to 39% and 30% to 13% of subjects, respectively. Prophylactic paracetamol had no clinically significant impact on the immune response to rMenB+OMV NZ or to the antigens in the routine vaccines Infanrix Hexa and Prevenar).

Therefore, the major options in terms of reducing the rate of fever appear to be either separating the administration of rMenB+OMV NZ from the administration of routine childhood vaccinations or giving prophylactic antipyretics.

There is also a response from the sponsor to the concern about febrile seizures raised by the EMA. Three febrile seizures were reported within 2 days of vaccination with rMenB+OMV NZ; in two cases, rMenB+OMV NZ was co-administered with Infanrix Hexa and Prevenar and in one case rMenB+OMV NZ was given alone. These events can be considered within the risk window for the post vaccination fever associated with rMenB+OMV NZ. One of these subjects had a complex febrile seizure and was discovered after enrolment to have significant underlying neurologic pathology with developmental delay. This subject was withdrawn from the study and subsequently experienced another apparent febrile seizure 5 months after this event. In the response to Day 120 questions from the EMA, Novartis states that: *"Based on these small numbers of cases, no definitive conclusions can be made with respect to increased risk of febrile seizure associated rMenB+OMV NZ vaccination in infants. There was no evidence from these studies, however, of an increased risk of febrile seizures following rMenB+OMV NZ vaccination. Some additional assurance can be gained from Study V72P13E1, in which no febrile seizures were reported within 9 days of vaccination of over 2200 toddlers with rMenB+OMV NZ. This is notable since febrile seizures are at a peak in the toddler age group."*

This assessment may currently be accurate, but more evidence in support of the absence of any excess attributable risk of febrile seizures needs large-scale post-marketing studies. Also, given the incidence of seizures and in particular febrile convulsions seen in these studies, the clinical evaluator recommended that either of these as pre-existing conditions would constitute a relative contra-indication to vaccination with this vaccine.

The EMA also requested further responses in relation to the cases of Kawasaki Disease seen in the studies. There was a panel of experts convened to assess all the reported cases and their relationship to study vaccine. Three cases occurred more than 30 days after vaccination and hence were thought unlikely to be related. One of the cases occurring within 30 days was thought unlikely to be Kawasaki Disease. Hence there were two cases meeting the case definition of Kawasaki Disease occurring within 30 days of vaccination. These are summarised below in Table 7.

Table 7. Summary of Suspected Cases of Kawasaki Disease in Studies V72P12 and V72P13 by Onset Interval ≤ 30 Days and > 30 Days from Last Dose of Study Vaccine

	Onset Interval from Last Study Vaccination	
Adjudication Outcome	≤ 30 days	> 30 days
rMenB+OMV NZ (N=4050*)		
Confirmed KD	2 (0.05%)	1 (0.02%)
Incomplete but likely KD	0	1 (0.02%)
Unlikely KD	1 (0.02%)	0
MenC or Routine Vaccines (N=1461*)		
Confirmed KD	0	1 (0.07%)

The incidence rates of Kawasaki Disease in Studies V72P12 and V72P13 appear to be higher than estimates obtained from other sources. However, annual incidence rates in children < 1 year of age are available for only a few selected European countries. Denmark, Finland and Ireland have estimated annual incidence rates of 4.5, 12 and 19.7 cases, respectively, per 100,000 children <1 year of age[32,33]. Given the very low numbers, interpretation of these differences is difficult. An important consideration is the very small population sizes and number of Kawasaki Disease cases in the rMenB+OMV NZ studies, resulting in highly unstable point estimates and wide confidence intervals. Also, the age group studied (infants <12 months of age) has the highest incidence rates of Kawasaki Disease and cases are not always reported.

In the response to the EMA concerns, Novartis also reports that three vaccines that have been licensed for use in U.S. infants in the past decade (Prevnar, Rotateq, and Rotarix) were all associated with higher rates of Kawasaki Disease in comparison to controls during pivotal studies, which led to the requirement of detecting Kawasaki Disease as a specific outcome of interest in large-scale post-marketing safety studies. It may be that the elevated rates of Kawasaki Disease observed in clinical studies of rMenB+OMV NZ and other recently licensed paediatric vaccines most likely reflect enhanced and complete case detection, including detection of incomplete Kawasaki Disease cases as well. Novartis states that *"there is currently no clear evidence to support a causal relationship between Kawasaki Disease and rMenB+OMV NZ vaccination. As such, Novartis does not believe that the observed Kawasaki Disease cases affect the safety of rMenB+OMV NZ vaccine nor do they impact the evaluation of the risk/benefit of the product. As with other recently launched paediatric vaccines, Novartis does acknowledge that Kawasaki Disease should be followed as an outcome of interest in large-scale post-marketing safety studies of rMenB+OMV."* Obviously this needs to be seriously and properly followed in large post-marketing studies of this vaccine as well.

List of questions

The clinical evaluator did not raise any questions in relation to the evaluated clinical data.

Recommendation regarding authorisation

Approval is recommended subject to definitive information regarding the post-marketing studies relating to the safety issues raised above. These 'enhanced pharmacovigilance' studies are necessary to provide assessment of specific adverse events. Also, the

[32] Fischer *et al*. KD incidence in Finland. *Pediatr. Infect. Dis. J*. 2007:26:411-415.
[33] Lynch M., Holman R.C., Mulligan A. *et al.* Kawasaki syndrome hospitalizations in Ireland, 1996-2000. *Pediatr. Infect. Dis. J.* 2003:22:959-962.

Australian MATS data is currently very limited and only available for 172 specimens collected between 2009 and 2011. This should be extended and more data provided to confirm the likely relevance of the vaccine serotypes in Australia. Post-marketing studies will also be necessary to demonstrate the clinical effectiveness of the vaccine in settings with high population coverage.

Revisions were recommended to statements in the draft PI and CMI; details of these are beyond the scope of the AusPAR.

Supplementary clinical evaluation

Following review of the clinical and quality evaluation reports, the TGA Delegate requested the sponsor address the following questions so that claims in relation to the newly developed potency assay and method for monitoring bacterial endotoxins (see *Quality*, *Summary of evaluation and issues of importance*, above) could be evaluated.

Question 1: [In the submission, it is stated that] an interim report for Study V72P16 is available. Please submit the most recently available interim report for clinical Study V72P16 or identify its location in the dossier.

Question 2: The quality data package does not contain batch analysis data of lots tested to the final specifications, nor does it contain real-time stability data showing compliance with the final specifications for even a small proportion of the proposed shelf life. By way of addressing these issues, reference is made to data from 2 clinical studies: V72P16 and V72_41. An interim report for Study V72P16 was submitted but Study V72_41 has not been submitted to the TGA and thus, the claims in support the proposed 24 month shelf life for Bexsero on the basis of clinical data (see *Quality*, *Summary of evaluation and issues of importance*, above)cannot be fully verified. Accordingly, you are requested to submit the report for Study V72_41 for evaluation.

The Supplementary CER provides an assessment of Studies V72P16 and V72_41.

Background

In order to address TGA concerns about the absence of real-time or accelerated stability data, the sponsor claimed that clinical data from two studies, V72P16 and V72_41, provide interim evidence of the potency of the vaccine and acceptably low endotoxin levels over the duration of the proposed shelf-life as follows:

- Vaccine lots used beyond their proposed 24-month shelf-life have been shown to be clinically effective:
  - An old Lot was used at a median age of 27 months in clinical Study V72P16 and gave an acceptable protective immune response.
  - A further Lot had a median age of 29 months when used in clinical Study V72_41 and gave an acceptable protective immune response in comparison with the reference lot (median age of 15 months). The reference lot is the current reference standard for the potency assay.
- Clinical vaccine was potent at half-dose, based on the fact that the Lot used at half-dose in clinical Study V72P16 was demonstrated to be non-inferior to a full dose. This observation was used to support the proposed release and stability specifications for potency tested by the potency assay.

In addition, it was argued that all lots of vaccine used in clinical trials have been shown to be safe. This claim was used to justify the bacterial endotoxins specification and the use of the modified *in vivo* rabbit pyrogen test (RPT).

An interim Company Study Report (CSR) for Study V72P16 was submitted to the TGA and evaluated in the first round CER. It included data collected 1 month after the primary vaccination series but not data for the booster or 12 month immunogenicity (secondary objectives). In the CER (above) the Study was evaluated in the context of rates of fever and the ability of paracetamol to reduce the rate of fever without adversely affecting the immune response in vaccinees. A CSR for Study V72_41 was not submitted to the TGA as part of the original application and was submitted at the request of the TGA. The purpose of this supplementary clinical evaluation was to review the design, conduct and results of studies V72P16 and V72_41 to confirm the veracity of the sponsor's claims.

Conclusions

Vaccine from an older lot (median age 27 months) when administered as a full dose to infants was found to result in an acceptable immune response as measured by the proportions of subjects with hSBA titres ≥ 1:5 against each of the 3 reference strains 44/76, 5/99 and NZ98/254 at 1 month post vaccination, and GMTs and geometric mean ratios (GMRs) at the same time point. The results were also consistent with those observed when vaccine from a lot with median age 16 months was administered under similar conditions in Study V72P12.

Administration of a full dose of an older lot (median age 29 months) to adolescents in Study V72_41 gave a comparable immune response to that of a younger lot (median age 15 months) as indicated by ratios of GMTs for the two lots falling within the requisite equivalence interval of 0.5 to 2.0 for each of the 3 reference strains. The GMT and GMR responses for the older lot against the reference strains were also comparable to that of the younger lot.

Whilst the overall results for the older lot were consistent with an acceptable immune response, some aspects of the immunogenicity of the younger lot (the reference lot) are of concern. In particular, the lower bound of the 95% confidence interval (CI) for the proportion of subjects achieving a titre ≥ 1:5 against reference strain NZ98/254 with the reference lot was only 62% (below the 70% threshold considered to be an acceptable immune response in the pivotal study in infants) and the proportion of subjects with a 4-fold increase in hSBA titre from baseline against NZ98/254 was 74%, compared to 85% for the older lot.

The reference lot was chosen as the reference standard for the modified potency assay and Study V72_41 was the first clinical study in which it had been used. It is also of note that the results achieved with respect to immunogenicity against reference strain with NZ98/254 in Study V72_41 were much lower than observed in the only other study involving adolescents (V72P10), even when the much higher prevalence of functional antibodies at baseline in that study was discounted. The higher baseline titres might be explained by the fact that Study V72P10 was conducted in Chile where subjects may have been more likely to have had prior exposure to colonising bacteria with antigens that cross-reacted with those of the serogroup B test strains.

Overall, the clinical data appears generally supportive of the sponsor's claim that lots used beyond the proposed 24 month shelf life gave acceptable protective immune response. No particular safety issues were evident from the use of aged lots. However, the actual data are quite limited. The sponsor should comment specifically on the immunogenicity results obtained for the reference lot in this study and the implications of this for its use as the reference standard for the potency assay.[34]

[34] This was addressed in the sponsor's response to the Delegate's Overview. See *Overall conclusion and risk/benefit assessment Response from Sponsor* below.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP version 2.0, data lock point 2 December 2010 + Australian specific Annex (ASA) dated 12 June 2012)) which was reviewed by the TGA's Office of Product Review (OPR). A summary of the RMP is shown in Table 8.

Table 8. Summary of proposed pharmacovigilance activities for potential risks and risk minimisation activities

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine* and additional)
Important identified risks:		
Fever (and complications such as Febrile Seizure)	Routine PV for fever but enhanced PV for febrile seizure	PI and Consumer Medicine Information (CMI) for the management of the fever
Important potential risks:		
Guillain-Barré Syndrome	Enhanced pharmacovigilance with questionnaire and adjudication by NVD SMT**	PI and CMI
Acute disseminated encephalomyelitis	Enhanced pharmacovigilance with questionnaire and adjudication by NVD SMT	PI and CMI
Anaphylaxis and Anaphylactic Shock	Routine pharmacovigilance	PI indicates that vaccine should not be given to persons with history of allergic reactions to the vaccine or its components.
Kawasaki Disease	Enhanced pharmacovigilance with questionnaire and adjudication by expert panel	PI and CMI
Seizure and febrile seizure	Enhanced pharmacovigilance with questionnaire and adjudication by NVD SMT	PI and CMI
Chronic Fatigue Syndrome	Routine pharmacovigilance	PI and CMI
Important missing information:		
Vaccine failure	Enhanced pharmacovigilance with SMT adjudication on pre-establish criteria	PI and CMI
Safety of vaccine during pregnancy or lactation,	Pregnancy registry	PI and CMI
Vaccine effectiveness	Vaccine effectiveness study	PI and CMI
Strain/serotype replacement	Carriage study	PI and CMI

*The terms PI and CMI, respectively, are used in place of 'SPC' (Summary of Product Characteristics) and 'Patient leaflet' that appear originally in the sponsor's RMP summary table. ** NVD SMT: Novartis Vaccines and Diagnostics Safety Management Team

Table 9 summarises the OPR's evaluation of the RMP, the sponsor's responses to issues raised by the OPR, and the second round OPR evaluation of the sponsor's responses.

Table 9. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
According to the European Public Assessment Report (EPAR) the RMP accepted in the EU is version 4. The sponsor should confirm if version 4 will be implemented fully in Australia and clarify the key differences between that version and version 2 which is evaluated in this report.	In their response the sponsor confirmed that they will implement the Bexsero EU RMP version 4 in Australia. They have provided a list of key differences between version 4 and the evaluated version 2.	This is acceptable.
It is recommended that consideration should be made for removal of a potentially misleading statement in the RMP regarding the sponsor's conclusion for no evidence of an increased risk of seizures.	*Data from clinical trials do not show an increased risk of febrile or non-febrile seizures associated with Bexsero vaccination compared to the control group.* *Although the Clinical Development Plan of Bexsero does not include any study powered to detect a statistical difference for rare and uncommon adverse events (and febrile seizures are just one possible uncommon event), the number and age distribution of febrile seizures observed in these studies is within the expected range in all age populations. In summary, although definitive conclusions based on these observations cannot be made due to the relatively small number of cases, the foregoing analyses provide no evidence of an increased risk of febrile or non-febrile seizures associated with Bexsero vaccination.*	At present the following statement in version 4 of the EU-RMP is considered satisfactory: *In summary, although definitive conclusions based on these observations cannot be made due to the relatively small number of cases, the foregoing analyses provide no evidence of an increased risk of febrile or non-febrile seizures associated with 4CMenB vaccination in infants.* That said, the evaluator still considers that the rates of fever seen in clinical trials should be clearly communicated to prescribers in the PI.
In the version 4 of the RMP accepted in the EU, there are several additional ongoing safety concerns according to the EPAR. These include the important potential risk 'decrease(d) immunogenicity after prophylactic use of paracetamol' and important missing information 'elderly', 'immunocompromised subjects', 'chronic medical condition patients' and 'compliance in adolescent and young adult(s)'. In the absence of a justification for their exclusion, it is recommended that these risks, and their associated pharmacovigilance and risk minimisation plans as specified in the EPAR are added to the RMP and/or ASA.	*Novartis is committed to implementing in Australia the EU RMP version 4, which contains the important potential risk 'decrease(d) immunogenicity after prophylactic use of paracetamol' and the important missing information 'elderly', 'immunocompromised subjects', 'patients with chronic medical conditions' and 'compliance in adolescent and young adult(s)'.*	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
The sponsor should provide the TGA with a commitment and assurance that the post-license study program will be undertaken as described wherever inclusion on a National Immunisation Programme (NIP) may first occur, including Australia.	*Novartis has planned safety (V72_36OB) and effectiveness (V72_38OB) studies and a study to monitor use of Bexsero during pregnancy (V72_39OB) as part of a national immunization programme (NIP).* *We agreed to submit proposals for plan B safety and effectiveness studies in another appropriate country with the next version of the updated RMP. The intent would indeed be to perform these plan B studies wherever inclusion on a NIP may first occur or in an "early launching country", not restricting solely to Europe. However, such proposals would also depend on other factors, such as the vaccine coverage (if outside of a NIP), the number of meningococcal disease cases, the willingness of the public health institute to collaborate with industry for effectiveness, and/or the availability of an appropriate study setting to assess safety; all with the purpose to ensure meaningful results within the shortest feasible time*	The proposed pharmacovigilance program is critical to the RMP for this product. The evaluator accepts that undertaking these activities where uptake of the vaccine is large (such as inclusion on a NIP) is necessary to ensure sufficient numbers. It is recommended that a contingency pharmacovigilance plan be provided to and agreed with the TGA if the proposed studies have not commenced within 12 months of product registration. The sponsor should keep the TGA regularly informed of the commencement/ progress/deferral of these studies (including the 'plan b' studies if applicable).
Additionally, as noted by the clinical evaluator the sponsor should also provide specific details of the entire confirmed study program including anticipated completion dates. This should also be detailed in an update to the RMP.	Requested details were provided.	The sponsor should keep the TGA regularly informed of the commencement/ progress/deferral of these studies (including the 'plan b' studies if applicable).
According to the ASA the sponsor is exploring ways to adopt the V72_38OB effectiveness study in Australia. If this application is successful it is recommended that this study is conducted in Australia as part of the pharmacovigilance plan. Other assurances regarding V72_38OB were also raised.	Requested details were provided	Sponsor responses regarding questions and assurances on Study V72_38OB are acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
It is recommended that the sponsor formulate and implement an education program for healthcare professionals and patients/caregivers. Given the sponsor has not proposed an education program the Delegate may wish to make implementation of an education program acceptable to the TGA a condition of registration for this product.	*Novartis commits to implementing an Australian education programme for Healthcare Professionals (HCPs; i.e. prescribers, pharmacists and nurses) and patients and their caregivers for Bexsero.*	It is recommended that details of the education programme including education materials should be provided to and agreed with the TGA prior to registration. Otherwise it is recommended to the Delegate that provision of an education programme satisfactory to the TGA is included as a condition of registration. The education programme may be referred to the Advisory Committee on the Safety of Vaccines (ACSOV) regarding its utility as an additional risk minimisation activity.
The sponsor should confirm whether the 'patient leaflet' refers to the 'consumer medicine information' or another, novel document. If it does refer to the CMI this should be made clear. It would be expected that some sort of patient/caregiver document such as that described in response to the TGA request for information is included as part of the education program (discussed above).	*Novartis confirm that the 'patient leaflet' does indeed refer to the 'consumer medicine information'.*	This is acceptable.
Several changes to the PI were recommended regarding the important identified risk 'fever' and important potential risk 'febrile seizure' as well as the prophylactic antipyretic statements.[35]	The sponsor's response included discussion of each recommended revision.	The evaluator's comments regarding the sponsor's response to each PI recommendation were conveyed to the Delegate.

[35] Details of PI and CMI text and recommended revisions are beyond the scope of the AusPAR.

Outstanding issues

Issues in relation to the RMP

The sponsor has agreed to formulate and implement an education programme. The educational materials and other details of the education programme should be provided to and agreed with the TGA. This should occur prior to approval. Otherwise it is recommended to the Delegate that this be made a condition of registration for this product.

The additional pharmacovigilance activities are entirely dependent the inclusion of Bexsero into a National Immunisation Program (NIP). Currently the location and commencement of these studies remains hypothetical. The sponsor should regularly update the TGA of the progress of the implementation of the pharmacovigilance plan. It is recommended that if the proposed studies do not commence within 12 months of approval a contingency pharmacovigilance plan should be provided to and agreed with the TGA.

Regarding routine risk minimisation, the evaluator has recommended PI changes relating to the important identified risk 'fever' and important potential risk 'febrile seizure'. These recommendations are maintained from the RMP evaluation report.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was sought for this submission and was incorporated into the RMP evaluation report.

Key changes to the updated RMP

In their response to the RMP evaluation report the sponsor provided an updated RMP (version 4, data lock point 1 September 2012, release date 12 November 2012) and ASA (dated 6 May 2013). According to the sponsor the following changes were made in the updated version:

Table 10. RMP version 4 updates from version 2.0

Safety specification	Clinical trial exposure data was updated through 1 September 2012. The total number of subjects who received at least 1 dose of Bexsero increased to 7812. The following potential risks were added: · OMV and aluminium risk · Decrease of immunogenicity secondary to use of paracetamol and other antipyretics. The following important missing information was added: · Elderly subjects · Immunocompromised subjects · Chronic medical condition patients · Compliance in adolescent and young adult
Pharmacovigilance activities	Nil significant change
Risk minimisation activities	Nil significant change

OPR Evaluator's comments:

Version 4 of the EU-RMP is the version that was accepted by the EMA at the time of approval in the EU.

According to the sponsor 'OMV and aluminium risk' has been added as an important potential risk. Although it is discussed in the safety specification it does not appear in the summary of ongoing safety concerns in the EU-RMP; this should be amended.

Summary of recommendations

If approved, the OPR recommended the following:

- Implement Bexsero EU-RMP (version 4, data lock point 1 September 2012, release date 12 November 2012) with Australian Specific Annex (dated 6 May 2013) and any future updates as a condition of registration.
- Conditions of registration regarding the education programme and additional pharmacovigilance activities may also be considered (see above).
- Implement conditions of registration regarding the provision of Periodic Safety Update Reports.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Novartis Vaccines and Diagnostics Pty Ltd has applied to register multi-component meningococcal B vaccine (recombinant, adsorbed) suspension for injection 0.5 ml pre-filled syringe. One dose (0.5 mL) contains 50µg of each of 3 recombinant *N. meningitidis* Group B proteins and 25 µg OMV measured as the total amount of protein.

The proposed therapeutic indications are:

> *"BEXSERO is indicated for active immunization against invasive disease caused by N. meningitidis group B strains. See Pharmacology for information on protection against specific 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."*

The proposed dosage regimen is summarised in the table below:

Table 11. Proposed Bexsero dosage regimen

Age Group	Primary Immunisation	Intervals between Primary Doses	Booster
Infants, 2 months to 5 months	Three x 0.5 mL	Not less than 1 month	Yes, 1 dose between 12 and 23 months
Infants, 6 months to 11 months	Two x 0.5 mL	Not less than 2 months	Yes, 1 dose between 12 and 23 months
Toddlers and Children, 12 months to 10 years	Two x 0.5 mL	Not less than 2 months	Need not established
Individuals, 11 years to 50 years	Two x 0.5 mL	Not less than 1 month	Need not established

The vaccine is to be given by deep IM injection.

Background

The current submission seeks registration of Bexsero, a vaccine developed to provide active immunisation for individuals from 2 months of age against invasive disease caused by *N. meningitidis* serogroup B.

Meningococcal disease

N. meningitidis is a human-specific pathogen that commonly colonises the nasopharynx of healthy adolescents and adults and produces either mild pharyngitis or no symptoms at all. Invasive meningococcal disease (IMD) is a rare and life-threatening disease that occurs when there is transmission of the bacterium to a susceptible individual. Invasive meningococcal disease most usually presents as either bacterial meningitis or meningococcal septicaemia, although occult bacteraemia, pneumonia, septic arthritis, conjunctivitis, and chronic meningococcemia can also occur. Invasive meningococcal disease occurs worldwide, with most disease being caused by 5 of the 13 serogroups of *N. meningitidis*: A, B, C, W-135 and Y.

Historically, *N. meningitidis* serogroups B and C have been the major cause of IMD in Australia. The introduction of the conjugate serogroup C meningococcal vaccines has dramatically changed the epidemiology of the disease in many developed countries, including Australia, leaving serogroup B as the predominant cause of invasive disease. According to the National Notifiable Diseases Surveillance System, in 2009 there were 259 notifications of IMD in Australia (at a rate of 1.2 per 100,000). Eighty-six per cent of those notifications had serogroup data available of which 88% were caused by serogroup B organisms. The highest rate for serogroup B infection was in the 0–4 years age group (5.2 per 100,000 population) followed by a peak in children from 15–19 years of age (2 per 100,000 population).[36]

Mortality rates for serogroup B disease in Australia have been estimated at approximately 0.06 per 100,000.[37] IMD also results in severe debilitating disease among survivors, with approximately 10-30% of patients suffering permanent sequelae including hearing loss, significant neurological damage, limb amputation, skin scarring, renal failure and cognitive deficits. Accordingly, the absence of a vaccine for *N. meningitidis* serogroup B remains an unmet public health need.

Bexsero multi-component meningococcal B vaccine

Vaccines against serogroup B meningococcus have been difficult to develop because the capsular polysaccharide of serogroup B is poorly immunogenic in humans, possibly due to similarities in serogroup B carbohydrate moieties to carbohydrates widely distributed in the human body. N-propionylated polysaccharide conjugates induce antibodies but without functional activity. Consequently, research has focused on proteins in the outer membrane of meningococci as potential antigens for vaccines. Bexsero has been developed using knowledge gained from other serogroup B vaccines based on protein-containing OMVs used in epidemics in Norway and New Zealand, together with advances from the identification of the *N. meningitidis* serogroup B genome sequence.

Bexsero contains four components that can be considered Drug Substances: three recombinant *N. meningitidis* Group B proteins identified by reverse vaccinology (two of which are fused to accessory proteins) and an OMV complex.

Quality

The manufacture of the recombinant proteins used in Bexsero is relatively straightforward. The NHBA and fHBP fusion proteins and the NadA are expressed via bacterial fermentation by standard recombinant DNA technology methods in *E. coli* using a

[36] Slaon-Gardiner T, *et al.* NNDSS Annual Report Writing Group. Australia's notifiable diseases status 2009: Annual report of the National Notifiable Diseases Surveillance System. *Communicable Diseases Intelligence* 2011:35(2): 61-131.
[37] Simpkins D, Wood N, Jelfs PB, *et al.* Modern trends in mortality from meningococcal disease in Australia. *Ped Inf Dis J* 2009:28(12): 1119-20.

plasmid vector system. The fourth component, OMV, is obtained from *N. meningitidis* through fermentation/culture expansion, inactivation and subsequent purification and filtration. The LPS/endotoxins that result from the fermentation of the *N. meningitidis* are part of the vesicles extracted from the bacteria, and play a role in the immunogenicity of the vaccine. Most LPS is removed during manufacture. Residual LPS is required to maintain the structural integrity of the proteins.

The evaluation of quality data was complicated and protracted mainly because the results of endotoxin testing and potency testing originally submitted to support the proposed shelf-life of Bexsero were generated by unacceptable methods:

- The quality evaluator found that the LAL test for endotoxin testing, as it had been performed, was not satisfactorily validated, was too variable and that the proposed final product endotoxins specification had not been satisfactorily justified. Consequently, several assay parameter changes were made to the LAL assay. Also, the proposed limit of the final product bacterial endotoxins specification was tightened from the previous level. The specifications contain a modified *in vivo* rabbit pyrogen test (RPT) in addition to the endotoxin test because of the pyrogenicity of the OMV component of the vaccine. The sponsor believes this test has the capacity to register the presence of non-endotoxin pyrogens in the product.
- The immunogenicity (potency) testing on the final product was originally proposed as a single-dose assay. The evaluator raised concerns about the ability of such an assay to give reliable differentiation between potent and sub-potent batches of vaccine. The unsuitability of the assay was acknowledged by the sponsor and a new multiple-dose relative potency assay was developed.

The evaluator considered the methodology, validation and variability of the new tests was acceptable, and the data confirmed consistency between clinical and commercial lots of vaccine for these tests. However, the implication of these changes is that there are no real-time or accelerated stability data to support the shelf life using the currently proposed methodologies. The sponsor has argued that several batches of vaccine used in clinical studies V72P16 and V72_41 were clinically effective when used at times in excess of 24 months after manufacture and provide interim evidence to justify the proposed shelf-life until appropriate stability data generated by the new potency and endotoxin tests are available. [Note: an interim Company Study Report (CSR) for Study V72P16 was submitted to the TGA and evaluated by the clinical evaluator. However, the study was evaluated only in the context of rates of fever and the ability of paracetamol to reduce the rate of fever without adversely affecting the immune response in vaccinees. A CSR for Study V72_41 was not submitted to the TGA as part of the original application and was submitted at the request of the TGA. Consequently, an assessment of both of these studies in respect of the quality issues was undertaken in a Supplementary CER.]

The evaluator also noted the proposed final product endotoxins specification, applied in conjugation with the modified *in vivo* rabbit pyrogens test, is orders of magnitude higher than limits applied to most paediatric vaccines. The endotoxin content of Bexsero derives from the OMV component and is therefore an intrinsic part of the formulation. In response to questions during the evaluation process about the safety of batches of vaccine with such levels of bacterial endotoxins the sponsor has sought to justify the proposed specification by reference to safety profiles of batches used in clinical studies. These two issues were considered to be beyond the scope of the Quality evaluation.

Pending clinical comment on the issues, the quality evaluator considered the application was approvable on the condition that the sponsor provides the TGA with stability data that will become available from ongoing studies and notifies the TGA of any results that could indicate a trend towards diminished potency over the 24-month storage period. The

PSC considered the retrospective use of the new assays was unacceptable and recommended that the decision regarding registration should be made on clinical grounds.

Nonclinical

The clinical formulation of the vaccine was tested in pivotal toxicity and reproductive and developmental toxicity studies, as well as other related developmental vaccines.

Active protection was not investigated due to the lack of animal models of infection. However, administration of the individual antigens and the clinical formulation to mice, guinea pigs, rabbits and non-human primates at doses ranging from a quarter to double the clinical dose proposed for humans demonstrated immunogenicity in terms of serum antibody (ELISA) and/or SBA titres. The vaccine protein antigens, with or without OMVs, were immunogenic in rabbits. Passive protection against bacteraemia by serogroup B strains was shown in infant rats administered antisera from vaccinated mice or guinea pigs.

No evidence of systemic toxicity was found in acute and repeat dose toxicity studies in which the clinical and related vaccine formulations were administered to rabbits at doses 1.3-2.1 times the dose proposed for a 5 kg infant, on the basis of bodyweight. However, there were small, significant increases in fibrinogen and globulin levels, and leukocyte and neutrophil counts, indicative of a transient immune/inflammatory response. Injection site reactions characteristic of an $Al(OH)_3$-adjuvanted vaccine were slightly more frequent and severe in vaccinated rabbits in comparison with controls, but within acceptable levels. Reproductive and developmental toxicity studies in female rabbits did not identify any clinically relevant negative effects.

The main toxicity consideration was that the vaccine contains a relatively large amount of LPS, which is highly pyrogenic in its free form. The nonclinical evaluator noted that the pyrogenicity of LPS is substantially reduced when associated with proteins in OMVs, and further reduced by adsorption of the OMVs to $Al(OH)_3$ adjuvant. However, a toxicity study with a related OMV vaccine reported elevated rectal temperatures in rabbits, indicative of residual pyrogenicity. Consequently, the nonclinical evaluator recommended that registration should be subject to satisfactory clinical investigation of vaccine pyrogenic potential, particularly in infants.

Clinical

The clinical evaluator has provided a detailed evaluation of a substantial amount of complex clinical data. An overview of the studies included in the clinical development program is located at Table 4, above.

Early studies (V72P1, V72P1E1, V72P2 and V72P3) were conducted using the first vaccine formulation containing the three recombinant meningococcal proteins, with or without OMV derived from the Norwegian strain 44/76 (OMV NW). Results from these studies were used to guide the subsequent development program and have not been included in the submission. Study V72P5 was the first to evaluate safety and immunogenicity of the final vaccine formulation.

Studies V72P4, V72P5 and V72P6 provided data for dose finding. Nine studies established the immunogenicity of the vaccine: 3 studies (V72P10, V72P4, and V72P5) in subjects 11 years of age and older (adolescents 11 to 17 years of age and adults 18 to 50 years of age); and 6 studies (V72P13, V72P13E1, V72P13E2, V72P12, V72P9, and V72P6) in infants and toddlers. Overall, data were available for 1503 vaccinated (from 1631 enrolled) adolescents 11 to 17 years of age, 81 adults 18 to 50 years of age, and 4843 infants 2 to 23 months of age exposed to at least 1 dose of the rMenB+OMV NZ vaccine. Of the 6555

subjects involved in the clinical development program, 1715 received a booster dose (either a third or fourth dose of vaccine). Three pivotal studies cover the two main intended populations – infants from 2 months of age (V72P13) and 12 to 15 months (booster/catch-up Study V72P13E1); and subjects aged 11 to 17 years (V72P10).

Immunogenicity has been assessed using a serum bactericidal assay with human serum as the source of exogenous complement (hSBA). This is a generally accepted scientific method for assessment of human immunity to the meningococcus.[38] The SBA measures levels of antibodies that recognise bacterial surface antigens and are capable of directing complement-mediated bacterial lysis, the main mechanism by which *N. meningitidis* serogroup B strains are killed after natural infection. A panel of 15 strains was used to test functional immune responses by hSBA in the early phase I studies. Subsequently, three "reference meningococcal serogroup B strains, NZ98/254, 44/76 and 5/99, were used. These reference strains are virulent strains isolated from cases of invasive disease. Strain NZ98/254 assesses bactericidal antibodies induced by the immunodominant PorA1.4 antigen in the OMV NZ; strain 44/76 assesses SBA induced by fHBP; and strain 5/99 for assesses SBA induced by NadA. An NHBA-specific ELISA assay was used to measure antibody responses against the NHBA *in lieu* of an appropriate, non-recombinant wild type strain. However, recently strain M10713 was identified as a suitable reference strain for evaluating NHBA-specific bactericidal killing and these data were presented where available.

The primary endpoint of the early clinical studies was the proportion of subjects with hSBA titres ≥ 1:4 against each of the reference strains. The sponsor chose a threshold of 1:4 because it had been shown that a naturally acquired hSBA titre of ≥ 1:4 provided protection against serogroup C among young adults[3] and efficacy data from Norwegian OMV vaccine trials suggested that hSBA titres ≥ 1:4 correlate with clinical efficacy.[39] However, in the Phase III studies V72P13 and V72P13E1 (but not the recent V72P10 Study) the threshold was set to a more conservative 1:5, as validation of the Novartis hSBA showed that the lower limit of the 2-sided 95% CI for a titre of 1:5 is a titre of 1:4, using linear interpolated hSBA titres. Other endpoints included hSBA GMT response and GMR to baseline.

Studies in infants and toddlers

- V72P13 was a large, well conducted pivotal, Phase III study conducted in 3630 infants aged 2 months at entry. Three injections of rMenB+OMV NZ were administered IM at 2, 4 and 6 months of age along with routinely administered infant vaccines (Infanrix Hexa and Prevenar). The study assessed the immunogenicity (hSBA titre) and safety of rMenB+OMV NZ and the consistency of the antibody response to 3 consecutively produced lots of rMenB+OMV NZ. Immune responses were considered acceptable if the lower limit of the 95%CI for the proportion of subjects with hSBA titres ≥ 1:5 for the 3 lots combined was ≥ 70%. Immunogenicity of the 3 lots was considered equivalent if the 2-sided 95% CI for the ratio of GMTs at 1 months after the 3 vaccinations for each of the 3 strains and each pair of vaccine lots fell within 0.50 to 2.00.

  Robust immunogenicity of rMenB+OMV NZ was observed in all treatment groups for all strains. The proportion of subjects with an hSBA titre ≥ 1:5 at 1 month following the third vaccination were 100% against each of the 44/76 and 5/99 strains and 84% against the NZ98/254 strain, with a lower limit of the 2-sided 95% CI ≥ 70% for all

[38] Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. *J. Exp. Med.* 1969:129(6):1307–26.
[39] Holst J, Feiring B, Fuglesang JE, *et al*. Serum bactericidal activity correlates with the vaccine efficacy of outer membrane vesicle vaccines against *Neisseria meningitidis* serogroup B disease. *Vaccine* 2003:21: 734–737.

strains for the three lots combined. Of particular note, response rates using SBA titres ≥ 1:8 were 72% against NZ98/254 and 100% against the 44/76 and 5/99 strains.

Antibody responses were also consistent from lot-to-lot of the vaccine, with the 2-sided 95%CI for the ratio of GMTs at 1 month after the third vaccination entirely contained within an interval of 0.74 to 1.33 for all three pairs of rMenB+OMV NZ vaccine lots for each strain.

The study was also designed to demonstrate that the immunogenicity and safety of routine infant vaccines (combined diphtheria and tetanus toxoids, acellular pertussis adsorbed (DTaP), inactivated poliovirus (IPV), hepatitis B (recombinant) (HBV), Haemophilus influenza type b (Hib) (that is, combined DTaP-IPV-HBV-Hib vaccine) and pneumococcal conjugate vaccine) when given concomitantly with rMenB+OMV NZ at 2, 4 and 6 months of age was non-inferior to that of routine vaccines given without rMenB+OMV NZ, where non-inferiority was defined as a lower limit (LL) of the 2-sided 95% CI for the difference in the proportion of subjects with antibody response ≥ a cut-off level pre-specified for that antigen was greater than -10%. Non-inferiority was demonstrated for diphtheria, tetanus, pertussis (pertussis toxin and filamentous hemagglutinin antigens), HBV, polio types 1 and 3, Hib antigens contained in Infanrix Hexa and the 7 pneumococcal antigens contained in Prevenar. However, non-inferiority criteria were not met for the pertactin component of pertussis vaccine (95%CI LL= -16%) and polio type 2 (95%CI LL=-11%).

- V72P13E1 was a booster/catch-up study conducted as an extension of Study V72P13. A total of 2249 toddlers who completed the parent study and who were then aged 12 months were randomised to receive a fourth (booster) dose of rMenB+OMV NZ with or without concomitant routine MMRV. Those subjects from the parent study who received routine immunisations only were randomised 3:1 to receive either MMRV alone at 12 months of age followed by 2 doses of rMenB+OMV NZ at 13 and 15 months of age or 2 doses of rMenB+OMV NZ, 1 at 12 months of age (with concomitant MMRV) and 1 at 14 months of age. The other control subjects from the parent study who received routine immunisations co-administered with Menjugate were randomised 1:1 to receive either a single dose of rMenB+OMV NZ together with MMRV at 12 months of age or a single dose of rMenB+OMV NZ at 12 months of age, followed by MMRV vaccination at 13 months of age. The 12-month booster produced a significant immune response in infants primed with a 3-dose primary course: 100%, 100% and 94%-97% subjects achieved hSBA ≥1:5 against reference strains 44/76, 5/99 and NZ98/254, respectively. The primary criterion for sufficient immune response (LL of the 2-sided 95% CI ≥ 75%) was achieved for all three reference strains. Also, both 2-dose schedules in naïve infants produced a response similar to that seen in the boosted primed infants. There was no interference with the responses to MMRV. Non-inferiority was not met for varicella using the seroprotection cut-off, although the difference in rates between groups was only 2%. The evaluator concluded that, as subjects had received only 1 of the 2 recommended MMRV doses, this finding is unlikely to be clinically important as the difference in seroprotection rates is minimal.
- V72P13E2 enrolled 508 subjects, comprising 392 subjects who had participated in the open-label extension Study V72P13E1. The study investigated antibody persistence 1 year after the booster dose given in V72P13E1, and booster response in toddlers 1 year after a 2-dose schedule administered in the second year of life. An additional group of 116 naïve subjects (defined as subjects who had never previously received any meningococcal B vaccine) approximately 24 months of age were recruited at the same study sites. Interim results demonstrated persistence of bactericidal antibodies at 1 year after the booster (fourth) dose of rMenB+OMV NZ administered at 12 months of age, as well as after 2 catch-up doses of rMenB+OMV NZ administered to toddlers at either 12 and 14 or 13 and 15 months of age. rMenB+OMV NZ was also found to be

highly immunogenic when given as a booster (third) dose at 1 year after a 2-dose catch-up schedule in toddlers.

- V72P12 was a large, well conducted Phase IIb study comparing different vaccination schedules and non-interference with routine vaccinations, involving 1885 infants aged 2 months at entry. rMenB+OMV NZ was administered using doses either 1 or 2 months apart, commencing at 2 months, either concomitantly or separated from other childhood vaccinations. Overall, there was a robust and sufficient bactericidal antibody response observed after 3 doses of rMenB+OMV NZ in all groups. The immunogenicity results were considered to support the use of rMenB+OMV NZ, either with or without concomitant routine infant vaccines, using either the 2, 4 and 6-month schedule or the accelerated 2, 3 and 4-month schedule.
- V72P9 was a small supporting Phase II study in which 60 older infants aged 6-8 months at entry were randomised 1:1 to receive 3 doses of rMenB either with or without OMV NZ at enrolment, 2 months later and at 12 months of age. rMenB+OMV NZ was shown to effectively induce bactericidal antibodies following 2 doses at approximately 6 and 8 months of age, as measured by hSBA against strains 44/76, 5/99 and NZ98/254. The third dose administered at 12 months of age resulted in higher GMTs compared to the second dose for strains 5/99 and NZ98/254.
- V72P6 was a small supporting Phase II study in which 147 infants aged 2 months at entry were enrolled and randomised 2:2:1:1 ratio to receive either rMenB or rMenB+OMV NZ (administered at 2, 4, 6, and 12 months of age) or a single dose of rMenB or rMenB+OMV NZ at 12 months of age. Six months after the third dose the subjects received a fourth dose and were followed up for a further 6 month period. rMenB+OMV NZ was shown to effectively induce bactericidal antibodies in infants following 3 doses at 2, 4 and 6 months of age. The responses could be further boosted with a 4th dose of rMenB+OMV NZ at 12 months of age, demonstrating that the infants had been primed with the 3 doses and immunological memory had been generated. This study provided sufficient evidence of immune responses to warrant the further development and evaluation of the rMenB+OMV NZ vaccine in infants in the phase 3 studies.

Studies in adolescents and adults

- V72P10 was a large, well conducted, pivotal, Phase IIb/III study in which 1631 adolescents (11 to 17 years of age) were randomised to receive either placebo or rMenB+OMV NZ in a 1-, 2- or 3-dose schedule in order to evaluate the optimal vaccination schedule in an adolescent population. The multidose schedules investigated were 2 doses given 1, 2 or 6 months apart, 3 doses given 1 month apart, or 3 doses given at months 0, 1 and 6 or months 0, 2 and 6. rMenB+OMV NZ was highly immunogenic for all vaccination schedules. The response was lower with a 1-dose schedule, whilst a 3-dose schedule did not add to the responses seen with the 2-dose schedule, both in terms of proportions of subjects with hSBA≥ 1.4 and for hSBA GMTs, thus providing the basis for the proposed 2-dose regimen in this age group.
- V72P4 was a small Phase II, open-label study conducted in 54 at-risk laboratory workers aged 18 to 50 years routinely exposed to *N. meningitidis*. Three formulations of MenB vaccination were compared using a 3-dose schedule at 0, 2 and 6 months. rMenB+OMV NZ was shown to effectively induce bactericidal antibodies (irrespective of baseline titres) in adults following 2 doses at 0, and 2 months, as measured by hSBA against the three MenB reference strains, and that a third dose at 6 months may not provide added benefit. However, 59% subjects had major protocol deviations (including missing blood draws (56%), vaccination outside the window (20%) and missing any Men B vaccination (7%)).

- V72P5 was a small Phase I study conducted in 70 adults 18 to 40 years of age who were randomised 2:2:1 to receive 3 doses of rMenB+OMV NZ, rMenB+OMV NW, or rMenB administered on a 0, 1-, and 2-month schedule. Immunogenicity was evaluated against a panel of fifteen *N. meningitidis* serogroup B strains including the 3 reference strains chosen for the Phase II and phase III studies. The proposed commercial formulation rMenB OMV NZ was more immunogenic than rMenB OMV NW, and both were more immunogenic than the vaccine without OMV. This was the basis for the use of rMenB OMV NZ in subsequent studies.

Safety

Events of special interest occurring within 6 days after the day of injection (and assumed to be at least possibly related to the administration of the study vaccine) were solicited and used as indicators of reactogenicity. These included *local reactions:* tenderness, erythema, swelling and induration; *systemic reactions:* change in eating habits, sleepiness, unusual crying, vomiting, diarrhoea, and irritability, rash; and *other indicators of reactogenicity:* body temperature (and fever defined as axillary temperature ≥38.0°C), and use of analgesic/ antipyretics.

The key safety findings in the infant and toddler studies were:

- a very high incidence of mild or moderate local reactions at the injection site, comprising tenderness, erythema and induration. However, most of these reactions were transient and resolved within the 7 day observation window. Other than for tenderness, severe local reactions were infrequent;
- injection site reactions were more frequently reported in infants receiving rMenB+OMV NZ with concomitant routine vaccines (Infanrix Hexa and Prevenar) than those receiving MenC vaccine with concomitant routine vaccine or routine vaccines only;
- local reaction rates for rMenB+OMV NZ were consistent across dose number in the schedule;
- systemic reactions were very common following vaccination with rMenB+OMV NZ, although most were mild or moderate in nature. Apart from rash, the rates of solicited systemic reactions were higher in infants administered rMenB+OMV NZ concomitantly with routine vaccines at the 2, 4, 6-month schedule (up to 86%) compared to those subjects receiving MenC vaccine with routine vaccines or routine vaccines alone. Most of the systemic reactions occurred within the first 3 days and were transient, with few continuing past the day 7 observation window. As for the local reactions, there was no apparent cumulative effect of the booster dose of rMenB+OMV NZ; and
- fever was reported in a high percentage of infants and was more frequently reported after receiving rMenB+OMV NZ with routine vaccinations (69-79%) than after routine vaccinations only (44-59%) and after routine vaccinations concomitantly administered with MenC vaccine (42-63%) across studies V72P12 and V72P13. Of note, in infants, the highest rate of fever after rMenB+OMV NZ was observed at 6 h post-vaccination and its duration was transient, resolving for most of the subjects by 48 h after vaccination on day 3. Also of note, in these studies parents were discouraged from administering prophylactic antipyretics in order to derive more accurate fever rates.

  An interim report for Study V72P16 (submitted during the course of the TGA's evaluation) suggested that fever associated with rMenB+OMV NZ can be reduced by prophylactic use of paracetamol just before administration of rMenB+OMV NZ + routine vaccines. The percentage of subjects reporting fever after any dose (fever ≥ 38.0°C) reduced from 88% to 76%, and fevers ≥ 38.5°C and ≥ 39.0°C were reduced

from 69% to 39% and 30% to 13% of subjects, respectively. Importantly, prophylactic paracetamol had no clinically significant impact on the immune response to rMenB+OMV NZ or to the antigens in the routine vaccines InfanrixHexa and Prevenar.

Other adverse events of significance observed in the infant/toddler studies (discussed in detail in the attached extract from the CER) were Kawasaki Disease, hypotonic episodes, and febrile and non-febrile seizures, as follows:

- 7 cases of suspected Kawasaki Disease were reported (6 in subjects who received rMenB+OMV NZ and 1 in a control subject who received MenC). Of the 6 cases occurring after vaccination with rMenB+OMV NZ, 3 were confirmed as Kawasaki Disease cases[40] by a panel of Kawasaki Disease experts and of these, 2 cases occurred within the 30-day post vaccination risk window used by the panel to attribute a biologically plausible causal association with vaccination and 1 of these 2 cases received rMenB+OMV NZ alone. Of the 3 remaining suspected cases, 1 was thought to be probable Kawasaki Disease, 1 was likely Kawasaki Disease and 1 was unlikely to be Kawasaki Disease and none were considered causally associated with vaccination (2 occurred more than 30 days after vaccination and 1 had onset of illness prior to vaccination with the first dose).

  Overall, the cases did not allow a definitive assessment of the causal relationship. The co-administration of rMenB+OMV NZ with other vaccines was a confounding factor in 5 cases.

- 2 cases of hypotonic hyporesponsive episodes met the Brighton Collaboration case definition.[41] One occurred within 1 day of vaccination with rMenB+OMV NZ co-administered with other vaccines and the other on the day of vaccination with routine vaccines Infanrix Hexa and Prevenar only. This gives rates of 8.4 episodes per 100,000 doses of rMenB+OMV NZ (administered with routine vaccines) and 16.3 episodes per 100,000 doses of the routine vaccines, which are both within the expected range for this condition in infants.

- 8 febrile seizures were observed in infants who received rMenB+OMV NZ (versus 2 in the control groups) in Studies V72P12 and V72P13. This is within the expected range for both groups. In the rMenB+OMV NZ group, 3 febrile seizures occurred within 2 days of vaccination with rMenB+OMV NZ and the remainder > 14 days post vaccination. rMenB+OMV NZ was co-administered with Infanrix Hexa and Prevenar in 2 of the 3 cases occurring within 2 days of vaccination (one case also had underlying neurological abnormalities); and rMenB+OMV NZ was given alone in the other. The number of non-febrile seizures (10 cases for both treatment groups) was also consistent with what would have been expected in this population. In the rMenB+OMV NZ groups, 4 of the seizures occurred within 3 days of vaccination - 3 where rMenB+OMV NZ was administered in combination with routine vaccines and 1 where rMenB+OMV NZ was administered alone; and 6 occurred >30 days post vaccination: 1 where rMenB+OMV NZ was administered in combination with routine vaccines (this child was subsequently found to have a ganglioglioma) and 5 where rMenB+OMV NZ was administered alone). Six febrile seizures and 1 non febrile seizure were observed in toddlers who received rMenB+OMV NZ with or without MMRV in the booster/catch-up Study V72P13E1. Three of the febrile convulsions occurred between 9 and 10 days post vaccination (2 with concomitant MMRV and 1 without). The remaining 3 febrile

[40] The diagnostic criteria applied by the Expert Panel are summarised in the CER (see Attachment 2 of this AusPAR).

[41] Buettcher, M, Heininger U, Braun M, Blumberg DA, Vermeer-de Bondt PE, Heijbel H *et al*. Hypotonic-hyporesponsive episode (HHE) as an adverse event following immunization in early childhood: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data .*Vaccine*. 2007:25:5875-81.

convulsions all occurred between 20-46 days post vaccination with rMenB+OMV NZ + MMRV. The non-febrile seizure occurred within 3 days of first vaccination without MMRV.

In the adolescent and adult studies, the key findings were:

- injection site pain was the most commonly reported local reaction after any rMenB+OMV NZ dose in both adults and adolescents, followed by erythema in adolescents and induration in adults. In the adolescent Study V72P10, all local reactions were reported less frequently after placebo than after rMenB+OMV NZ except for pain, which was similarly reported;
- malaise, myalgia and headache were the most commonly reported systemic reactions after any rMenB+OMV NZ dose in both adults and adolescents. In the adolescent Study V72P10, each systemic reaction was similarly or slightly less frequently reported after placebo than after rMenB+OMV NZ. Fever was similarly reported in the rMenB+OMV NZ and placebo groups (3%-5% and 2%-4% across vaccinations, respectively) and rates were low and similar for both adolescents and adults;
- the frequency of reports for local and systemic reactions was generally lower with subsequent administrations;
- most of the local and systemic reactions were mild or moderate in severity and were transient; and
- notwithstanding the limited numbers of adult subjects (that is, >18 years age) enrolled in the clinical program, the safety profile in adults appeared to be similar to that of adolescents.

Clinical evaluator's recommendation

The clinical evaluator considered there were sufficient immunogenicity and safety data to support registration of rMenB+OMV NZ vaccine but with some caveats:

- that 'enhanced pharmacovigilance' studies are necessary to provide assessment of specific adverse events such as Kawasaki Disease and febrile seizures;
- a history of neurological disease, seizures and, in particular, febrile seizures should be included as precautions in the PI and under such circumstances the vaccine should only be given under close medical attention; and
- the collection of Australian MATS data should be extended and more data provided to confirm the likely relevance of the vaccine strains in Australia (this is covered further under *Delegate considerations*, below).

In reaching this position the evaluator considered that rMenB+OMV NZ appears to be highly effective in inducing bactericidal antibodies in humans beginning from 2 months of age (although NHBA-specific bactericidal killing was only directly assessed in a small subset of participants in V72P13/ V72P13E1). These studies showed a high level of efficacy at 1 month following primary course of vaccination and there were data showing persistence of antibodies 12 months after the primary course in infants and toddlers.

Regarding risks, the evaluator noted the high rates of local and systemic reactions, and fever in infants when rMenB+OMV NZ was given with routine vaccines whereas when the rMenB+OMV NZ vaccine was given separately from routine vaccines the rates of local and systemic reactions appeared similar in both groups. Most cases of fever were noted to be categorised as mild or moderate, were transient, and did not lead to increased rates of health care utilisation or specific medical sequelae. Nevertheless it was considered important that fevers are adequately managed because febrile seizures peak in the toddler age group. The evaluator considered that the risk of fever could be managed in healthy

individuals through appropriate communication with the care giver and/or the use of prophylactic antipyretics, whilst in infants with a history of febrile convulsions, vaccination should be given under close medical attention and it may be worth taking special measures to further lower the risk of fever (such as separation from other vaccines). It was also concluded that large-scale post-marketing studies are needed for more definitive evidence of an absence of an increased risk of febrile convulsions.

Risk management plan

The TGA's OPR conducted an evaluation of the RMP proposed by the sponsor and referred the submission to the ACSOM for consideration.

Concerns were raised about the rates of fever and the potential for febrile seizures and Kawasaki Disease with Bexsero. Specifically with regard to fever rates, the ACSOM noted that subjects had received concomitant immunisation with 7-valent pneumococcal conjugate vaccine (7vPCV) rather that 13-valent pneumococcal conjugate vaccine (13vPCV) which is used on Australia's NIP. ACSOM advised there is evidence to suggest that 13vPCV has been associated with an increased risk of febrile seizures when given concomitantly with influenza vaccine in post marketing studies in the USA. Therefore there is a concern that, in the real world, the risk of febrile seizures could be increased if Bexsero is concomitantly administered with 13vPCV. It was also noted that there was an imbalance in the reporting of non-febrile seizures in the trials in which the risk of febrile seizures had been assessed and that the trials largely involved recipients who were infants and not toddlers (12-23 month olds), toddlers being most at risk of febrile seizures. In light of this and the foregoing point, the ACSOM concluded that the sponsor's proposed comment in the RMP that 'analyses provide no evidence of an increased risk of febrile or non-febrile seizures associated with 4CMenB vaccination in infants' was misleading. ACSOM concluded that, given the high proportion of subjects who experienced a high fever, the prophylactic use of antipyretics could be an appropriate measure to mitigate the risk of fever but it would not mitigate the risk of febrile seizures. It also advised that an educational program should be undertaken to inform health professionals of the risks associated with Bexsero, especially if the sponsor intends to market the vaccine prior to, or in the absence of, NIP listing. The sponsor has since indicated it is committed to implementing an educational program in Australia under the ASA to the RMP.

The sponsor has also proposed that seizure and febrile seizure, Kawasaki Disease, anaphylaxis/anaphylactic shock, Guillain-Barré syndrome and acute disseminated encephalomyelitis will each be the subject of enhanced pharmacovigilance activities (using questionnaire and adjudication) as well as a post-licensure observational safety surveillance study. The RMP evaluator's comments in regard to the pharmacovigilance plan in this context were endorsed by the Delegate.

Risk-benefit analysis

Delegate considerations

There are a number of limitations and issues with the clinical data:

- **No efficacy data have been submitted** and the efficacy of rMenB+OMV NZ in preventing IMD has been inferred from its ability to induce functional bactericidal antibodies directed against serogroup B meningococci. The Delegate accepts that efficacy trials are not feasible because IMD is rare and there are > 3,000 circulating strains of the bacterium. Thus, the challenge is one of predicting the potential effectiveness of the vaccine, or in other words how to show that rMenB + OMV NZ can kill meningococcal B bacteria, particularly those strains prevalent in Australia. The

gold standard, hSBA, is not feasible for routine screening because serum of vaccinees is limited and because of strain diversity. The sponsor developed MATS to predict whether a strain will be killed by antibodies induced by rMenB+OMV NZ. Preliminary MATS data from a survey of 172 invasive meningococcal serogroup B isolates collected during 2009-June 2011 showed that 76% (95%CI: 59 to 87%) of isolates had an antigen type covered by rMenB+OMV NZ.

More recent information provided by the sponsor following receipt of the TGA CER indicates that 76% (95%CI: 63 to 87%) of 373 invasive isolates collected between January 2007 and December 2011 across 5 Australian States (excluding Victoria) and 2 Territories were predicted to be killed in hSBA based on their MATS vaccine antigen type. Although the number of isolates tested to date remains low[42], it appears the vaccine will be effective against the majority of strains. Importantly, a vaccine effectiveness study is planned by the sponsor.

- The **duration of protection is currently unknown** as long term immunogenicity data are unavailable. Antibody levels against the PorA antigen (as assessed by hSBA ≥ 1:4 or 1:5 against reference strain NZ98/254) in infants and toddlers fall considerably from 1 month post third vaccine dose to 6 months post vaccine dose (Studies V72P6 and V72P13). The antibody levels against fHBP (measured by response against reference strain 44/76) also fall but to a lesser extent. However, there is clear evidence of immunological memory in subjects at 12 months of age *vis a vis* the return to high antibody levels 1 month after the booster dose (Study V72P13). Importantly, immunological memory has not been demonstrated in older age groups or after a 2-dose priming schedule or over longer periods and, consequently, there is uncertainty as to whether the vaccine will provide adequate levels of immunity for the full period over which infants/toddlers and adolescents are at greatest risk of IMD.
- The sponsor has proposed a 2-dose schedule administered at least 2 months apart for children from 6 months of age up to 10 years of age. However, apart from a limited number of rMenB+OMV NZ naïve subjects in Study V72P13E2 who received 2 doses of rMenB+OMV NZ 2 months apart at approximately 24 months of age (window 23-27 months), there were **no immunogenicity data for children aged between 2 and 10 years of age**. However, there were very similar robust responses to all vaccine antigens observed after a 2-dose schedule across older infants (Study V72P9); toddlers in their second year of life (Study V72P13E1) and adolescents (Study V72P10) and thus it seems reasonable that the same regimen could be used in children aged 2 to 10 years of age.
- **Very limited data are available in adults. Also, no data are available in the elderly or immunosuppressed individuals or those with chronic medical conditions**, the concern being that such individuals may either not mount a protective antibody response or have a differing safety profile. The absence of such data is mentioned in the proposed PI and RMP.
- **the proposed recommended dosage regimen in the 2-5 month age group allows for an accelerated schedule** with not less 1 month between doses (that is, using a 2, 3 and 4-month schedule). Immunogenicity data were acceptable with such a regimen and the safety profile appeared similar to that for the 2, 4 and 6-month dosing schedule. However, the number of subjects exposed to accelerated administration of rMenB+OMV NZ in that age group was only 318 (all in Study V72P12), which is a small safety population large enough to detect common adverse events (those occurring with frequency greater than 1%) but not large enough to detect uncommon or rare events.

[42] Sponsor comment: all invasive isolates available at the time were tested.

- **There are no data on strain-serotype replacement**. A nasopharyngeal carriage study has been proposed as a first step as part of the RMP.

Specifically with regard to safety, there is a high rate of mild to moderate local and systemic side effects indicative of reactogenicity following vaccination with rMenB+OMV NZ. As noted by the quality evaluator, the high endotoxin content of Bexsero derives from the OMV component and is therefore an intrinsic part of the formulation, with levels much higher than present in most paediatric vaccines. Fever ≥ 38°C occurs commonly with rMenB+OMV NZ and **rates of fever are very high when the vaccine is co-administered with routine childhood vaccinations** (in the order of 70-80%). The ACSOM had cause for concern that the rates could be even higher in the context of co-administration with 13vPCV. Of note, there are no clinical data on the concomitant use of Bexsero and 13vPCV.

This is a significant safety signal because of the consequent risk of febrile convulsions, particularly in toddlers being the age group most at risk of febrile convulsions. Febrile convulsions have the potential to disrupt the routine immunisation schedule and undermine confidence in the vaccine and in immunisation (and the NIP) more generally. The clinical evaluator considered there were two options for minimising the risk of fever: to include the prophylactic use of antipyretics; or by alternating the administration of rMenB+OMV NZ and other routine childhood vaccinations. However, the ACSOM considered the use of an intercalated schedule was not practical. Furthermore, ACSOM considered that the results of Study V72P16, in which fever rates were reduced by concomitant administration of paracetamol, may not be readily achieved in the real world because of the dosing regimen (6 hourly dosing) required but agreed that, in the absence of any other identifiable risk minimisation measures, the use of prophylactic antipyretics seems unavoidable.

The main point of contention is how the information about the potential for febrile reactions is to be presented in the PI and how the risks can be managed under the RMP through its risk minimisation activities. The sponsor has argued that although the risk of fever was increased, there was no evidence of an increased risk of febrile convulsions and therefore no specific advice was needed in the PI or RMP. However, as pointed out by both the clinical evaluator and the ACSOM, this situation is one of an absence of evidence rather than evidence of absence of risk. Indeed, the ACSOM stated "the data do not provide evidence of no risk, rather they are suggestive of risk, which prima facie is likely given the high frequency of high fever." The Delegate agreed with ACSOM's position and requested the sponsor to amend the PI and RMP to contain the information recommended by the RMP evaluator and ACSOM.

The remaining concern relates to the absence of real-time stability data to support the proposed shelf life of 24 months. Such data are not expected to be available until July 2013. However, the sponsor claims that clinical data from two studies, V72P16 and V72_41, provide interim evidence of the potency of the vaccine over the duration of the proposed shelf-life. These claims were assessed in a Supplementary CER. The key conclusions of that evaluation were:

- Vaccine from an older lot (median age 27 months) when administered as a full dose to infants gave an acceptable immune response as measured by the proportions of subjects with hSBA titres ≥ 1:5 against each of the 3 reference strains 44/76, 5/99 and NZ98/254 at 1 month post vaccination, and GMTs and GMRs at the same time point. The results were also consistent with those observed when vaccine from a lot with median age 16 months was administered under similar conditions in Study V72P12.
- Administration of a full dose of an older lot (reference lot; median age 29 months) to adolescents in Study V72_41 gave an immune response comparable to that of a younger lot (median age 15 months) used in the same study, as indicated by ratios of GMTs for the 2 lots falling within the requisite equivalence interval of 0.5 to 2.0 for

each of the 3 reference strains. The GMT and GMR responses for the older lot against the reference strains were also comparable to that of the younger lot. Whilst the overall results for the older lot were consistent with an acceptable immune response, some aspects of the immunogenicity of the younger lot (reference lot) were of concern. In particular, the lower bound of the 95% CI for the proportion of subjects achieving a titre ≥ 1:5 against reference strain NZ98/254 with the reference lot was only 62% (below the 70% threshold considered to be an acceptable immune response in the pivotal study in infants) and the proportion of subjects with a 4-fold increase in hSBA titre from baseline against NZ98/254 was 74% compared to 85% for the older lot. The reference lot has been chosen as the reference standard for the modified potency assay and Study V72_41 was the first clinical study in which it had been used. It is also of note that the results achieved with respect to immunogenicity against reference strain with NZ98/254 in Study V72_41 were much lower than observed in the only other study involving adolescents (V72P10), even when the much higher prevalence of functional antibodies at baseline in that study was discounted. Importantly, the sponsor should comment on the immunogenicity results obtained for reference lot and the implications of this for its use as the reference standard for the potency assay.

The clinical data for aged lots of Bexsero, albeit quite limited, appear generally supportive of the proposed 24 month shelf life in that older lots gave acceptable protective immune responses and no additional safety issues were evident with their use. Overall, there are sufficient clinical data to justify the proposed shelf-life in the absence of real time stability data. In the event of product approval, the conditions of registration proposed by the quality evaluator will be imposed.

Benefit-risk balance

The exact benefits of Bexsero in relation to its proposed indication can only be elucidated in the post marketing setting where a number of the uncertainties outlined above can be addressed in line with activities proposed in the RMP. Furthermore, the benefit is likely to be relatively small given that IMD is a rare disease in Australia. However, the impacts of the disease are significant, and the benefit of having a vaccine available in the event of outbreaks of disease would be greater. The available data indicates that Bexsero results in robust functional immune responses as measured by hSBA and from this and MATS data it is reasonable to expect the vaccine will be effective against the majority of strains.

Balanced against this is the fact that Bexsero is clearly pyrogenic, particularly when administered with routine childhood vaccinations. However, the available clinical data have shown that most cases of fever are mild or moderate and transient in nature. Nevertheless, fever needs to be adequately managed because of the consequent risk of febrile convulsions. This can be achieved through appropriate guidance for prescribers and education of and communication with care givers about the use of prophylactic antipyretics.

Proposed action

Overall, the Delegate is of the view that the product has a favourable benefit-risk balance. However, this is dependent on there being comprehensive information about the risks and management of fever and its sequelae in the PI and appropriate risk minimisation activities such as educational and communication programs implemented under the RMP. With regard to the latter, the sponsor was requested to negotiate a version of the RMP to the satisfaction of the OPR prior to finalisation of the application. Implementation of the final agreed version of the RMP will be imposed as a condition of registration in the event of product approval.

Request for ACPM advice

The Delegate sought general advice on this application from the ACPM and requested the committee provide advice on the following issues in particular:

- whether the immune responses measured by hSBA are sufficient to infer there will be acceptable protective efficacy against IMD. The ACPM was also requested to comment on the role and utility of MATS, a new tool unique to Bexsero, as a predictor of strain coverage;
- noting the absence of immunogenicity data for subjects aged 2 to 10 years, whether the use of regimen 2-dose regimen can be supported using data generated in younger and older age groups;
- whether there is sufficient evidence of immunogenicity and safety to support the use of an accelerated regimen (with dosing at 2, 3, and 4 months) in the 2 to 5 month age group;
- whether there is sufficient information about the risk of fever with Bexsero and the increased risk of febrile seizures following fever within the PI and RMP to ensure the safe use of Bexsero; and
- whether, *in lieu* of real time stability data, the clinical data from studies V72P16 and V72_41 provide sufficient assurance that the potency and stability of the vaccine remains adequate over the proposed shelf life of the product.

Response from sponsor

Introduction

Consistent with the assessment from the clinical evaluator, the Delegate acknowledges that the risk-benefit balance of Bexsero, given the proposed usage, is favourable. In particular, the Delegate notes that:

(a) the quality evaluator considers the application approvable on the condition that Novartis provides the TGA with stability data that will become available from ongoing stability studies and notifies the TGA of any results that could indicate a trend towards diminished potency over the 24 month storage period;

(b) the clinical evidence included in the submission presented sufficient immunogenicity and safety data to support registration provided that

> i.) enhanced pharmacovigilance studies were planned for specific adverse events (AEs) such as Kawasaki Disease and febrile seizures,
>
> ii.) the PI includes wording about history of neurological disease, seizures and febrile seizures in the Precautions section, and that
>
> iii.) the collection of Australian MATS data be extended; and that

(c) in line with the RMP evaluator recommendation, Novartis is committed to implementing an educational program in Australia to inform health professionals of the risks associated with the use of Bexsero. Novartis welcomes the Delegate's conclusions with regards to the Bexsero benefit risk balance and addresses below the comments and concerns raised in the Delegate's Overview. For the sake of clarity and convenience, the Delegate's comments are transcribed in italics throughout the response below.

Responses to comments and issues raised in the Delegate's overview

Efficacy

Overall the Delegate acknowledges that the benefits of Bexsero in relation to its proposed indication can only be elucidated in the post marketing setting, and that given that no

efficacy data were submitted, *the efficacy of rMenB+OMV NZ [Bexsero] in preventing IMD has been inferred from its ability to induce functional bactericidal antibodies directed against serogroup B meningococci*. The Delegate however requests the ACPM to comment on *whether the immune responses measured by hSBA [human serum bactericidal antibodies] are sufficient to infer there will be acceptable protective efficacy against IMD* and on *the role and utility of MATS, a new tool unique to Bexsero, as a predictor of strain coverage*. A hSBA titer ≥ 1:4 has been historically defined as the threshold titer that correlates to clinical protection against meningococcal disease. Evidence that support the importance of bactericidal activity in protection comes primarily from several observations:

(a) in the seminal study by Goldschneider and colleagues, investigators observed that subjects with hSBA titers of ≥ 1:4 who were exposed to a group C meningococcal epidemic did not develop disease while virtually all cases occurred in individuals whose baseline hSBA titers were < 1:4;

(b) this same group reported an inverse relationship between the average age of acquisition of naturally acquired serum bactericidal antibody against serogroups A, B and C and the incidence of meningococcal disease;

(c) the importance of serum bactericidal antibody in protection against meningococcal disease also is underscored by the greatly increased risk of acquiring meningococcal disease in persons with inherited complement deficiencies who lack serum bactericidal activity.

An evaluation of strain coverage afforded by Bexsero immunisation is hampered by the inability of current typing systems to account for the diversity in sequence and level of expression of the surface proteins used in the vaccine. Novartis therefore developed the MATS platform which combines conventional genotyping for PorA with a specialised sandwich ELISA that quantifies the relative expression and cross-reactivity of antigenic variants by Bexsero-induced antibody. The readout of the MATS ELISA is a relative potency (RP) against fHBP, NadA, and NHBA on individual strains. By correlating the killing of a panel of serogroup B strains with the MATS RP values, the he MATS method established a minimum level of RP for fHBP, NadA, and NHBA (the positive bactericidal threshold or PBT), which predicts whether a given MenB isolate would be susceptible to killing in the hSBA assay by antibodies induced by Bexsero.

To date, a survey of 373 invasive meningococcal group B isolates collected between January 2007 and December 2011 from five Australian states and two Territories showed that 76% (95% CI 63%-87%) of meningococcal group B isolates were predicted to be killed in hSBA based on their MATS vaccine antigen type. Novartis is committed to collect and test further Australian isolates to monitor the predictability of the vaccine effectiveness as well as to conduct a vaccine effectiveness study.

Data in subjects 2 to 10 years of age

Novartis acknowledges that only limited data (116 subjects 24 months of age enrolled in Study V72P13E2) for individuals aged 2 to 10 years was presented in the submission. However, as the Delegate also recognises, *there were very similar robust responses to all vaccine antigens observed after a two dose schedule across older infants (Study V72P9); toddlers in their second year of life (Study V72P13El) and adolescents (Study V72P10) and thus it seems reasonable that the same regimen could be used in children aged 2 to 10 years of age*. Immune responses to all vaccine antigens following a 2-dose primary schedule were consistently high in the younger (older infants and toddlers) and older (adolescents) contiguous age groups suggesting no reason to expect that the response in the 2 to 10 years of age would be greatly different. Consistent with this, recent data from extension studies not submitted to TGA (available upon request) which enrolled, among others, naïve subjects aged 24-26 months (56 subjects from Study V72P12E1), 40-42 months (84 subjects from Studies V72P6E1 and V72P9E1), or 60-62 months (99 subjects from Studies

V72P6E1 and V72P9E1) reconfirmed that bactericidal immune responses following the second vaccine dose were consistent with those reported in subjects from study V72P13E2 and in the range across the contiguous age groups. Overall, the data reviewed by the TGA sufficiently support a 2-dose schedule in the 2 to 10 years of age population.

Schedule 2, 3, 4 in infants 2 to 5 months of age

The Delegate acknowledges that the efficacy data available at the time of submission demonstrated acceptable immunogenicity on the accelerated schedule (2, 3, and 4 months of age schedule; Schedule 1) in infants 2 to 5 months of age but also highlights that *the number of subjects exposed to accelerated administration of rMenB+OMV NZ in that age group was only 318 (all in Study V72P12), which is a small safety population, large enough to detect common adverse events (those occurring with frequency greater than 1%) but not large enough to detect uncommon or rare events*.

It should be noted that further immunogenicity and safety data for infants vaccinated according to Schedule 1 have been generated in Study V72P16 which was submitted to the Delegate during the course of the evaluation. In this Study, an additional overall 552 subjects were exposed to Bexsero with (N=183) or without prophylactic paracetamol treatment (N=369). Overall the immune responses at 1 month after the third vaccination as measured by hSBA in terms of percentages of subjects with a titer ≥1:5 and of geometric mean titers for the three indicator strains H44/76, 5/99, NZ98/254 and by ELISA geometric mean concentrations for the NHBA vaccine antigen were very similar between subjects who received Schedule 1 with concomitant routine vaccines in studies V72P12 and V72P16 and the subjects who received a 2, 4, 6 schedule (Schedule 2) both in the same Study V72P12 and in Study V72P13. In particular, for each of the 3 indicator strains the lower limit of the 2-sided 95% CI for the percentages of subjects with a hSBA ≥1:5 was above the protocol prespecified cut-off (that is, ≥70% for Studies V72P12 and V72P13 and ≥65% for Study V72P16) associated with the primary immunogenicity objective.

The tolerability profile of Bexsero in Study V72P16 was similar to that seen with Schedule 2 in V72P12. However, in the V72P16 group receiving paracetamol, percentages of subjects with local and systemic reactions were lower than those who did not receive the prophylactic paracetamol. Importantly, data from this study provide evidence that when paracetamol is adopted prophylactically there is a statistically significant reduction in the percentage of subjects reporting fever following concomitant administration of Bexsero with routine infant vaccines. Rates of unsolicited AEs observed were similar between subjects who received Schedule 1 and Schedule 2. In particular, rates of serious AEs and of events of particular clinical interest such as seizures were observed with similarly low frequencies. Based on the above results, Novartis believes that the currently available data for Schedule 1 for overall 870 subjects exposed to Bexsero provides sufficient evidence to support the use of either of the proposed dosing regimen in this age group given the close similarity to the results obtained in infants vaccinated with the two schedules.

Importantly, Novartis received advice from the Australian Technical Advisory Group on Immunisation (ATAGI) on the schedule on 17 May 2013. The Australian advisory group on immunisation considers that, should Bexsero be included in the local NIP, concurrent administration with those vaccines currently used in the NIP at the schedule points of 2, 4, 6 and 12 months of age (that is, Schedule 2) is most appropriate.

Safety

The safety of Bexsero was evaluated in 9 studies including 7 randomised, controlled clinical trials with 6555 subjects (from 2 months of age) who received at least 1 dose of Bexsero. Among Bexsero recipients, 4843 were infants and toddlers, and 1712 were adolescents and adults. In infants and toddlers the most common local and systemic adverse reactions observed in clinical trials were tenderness and erythema at the injection site, fever and irritability.

Information on fever is currently included in the PI and the RMP. Considering the predictable characteristics of fever associated with Bexsero vaccination, that is, mostly mild or moderate, with early onset upon vaccination and of short duration, which was confirmed by the very low rates of medically attended fever observed in the clinical trials, Novartis is convinced that the risk of fever, and consequently of febrile seizures, can be adequately highlighted and managed through appropriate communication to Healthcare Professionals (HCPs). Given the relevance of the topic it is Novartis intention to continue to conduct further observations; a post-licensure observational safety surveillance study is already planned with the aim of identifying and characterising, among other events, rates of seizure.

Novartis believes the RMP and its Australian implementation adequately ensure the safe use of Bexsero and an update of the PI is not considered necessary. Novartis commits to implementing an educational program for HCPs (that is, prescribers, pharmacists and nurses) and patients and their caregivers as an additional risk minimisation activity. Educational material for HCPs will highlight the risk of fever and potential risk of febrile seizure. In addition, this material will also highlight guidance for prophylactic antipyretic treatment, including a statement that antipyretics other than paracetamol have not been studied for their impact upon immunogenicity, advice for patients on what to do if they experience adverse events following vaccine administration and information that Bexsero has not been specifically studied when given in combination with 13-valent pneumococcal vaccine will also be included.

Novartis will provide the TGA OPR with an updated version of the Australia RMP for review and approval. In the meantime, note that the proposed ASA of the RMP includes:

> "As with many vaccines, the health care professional should be aware that a temperature elevation may occur following vaccination of infants and toddlers. In infant Study V72P13, fever ≥ 38.0°C was reported by 78%, 84% and 73% of subjects after dose 1, 2 and 3, respectively, in the Bexsero vaccine group, compared with 44%, 59% and 50% of subjects receiving the routine vaccines alone. The rate of fever was decreased by the use of prophylactic antipyretics (as demonstrated in Study V72P16). Prophylactic administration of antipyretics at the time of 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 toddlers. Preliminary advice received from ATAGI favours a recommendation for prophylactic use of paracetamol in infants. The safety profiles of the co-administered vaccines were unaffected by concomitant administration of Bexsero with the exception of more frequent occurrence of fever, tenderness at the injection site, change in eating habits and irritability. 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.
>
> While no evidence of increased risk for febrile seizures was seen in clinical trials for Bexsero, several other vaccines with a fever profile have been shown to increase the risk of febrile seizure in post-marketing settings; therefore, caution should be employed in administration of Bexsero to persons with individual or family history of convulsions, including febrile convulsions."

Finally, Novartis acknowledges that the implementation of the final agreed version of the RMP will be imposed as a condition of registration in the event of product approval.

Shelf-life and reference standard for potency assay

Upon review of the clinical data provided, the Delegate acknowledged that *the clinical data for aged lots of Bexsero, albeit quite limited, appear generally supportive of the proposed 24 month shelf-life in that older lots gave acceptable protective immune responses and no*

additional safety issues were evident with their use. Overall, there are sufficient clinical data to justify the proposed shelf-life in the absence of real time stability data. Nonetheless, with regards to the data in Study V72_41 showing a decrease in responders to the reference strain NZ98/254 among the subjects vaccinated with the reference lot ("Lot A"), it was suggested that *the sponsor should comment on the immunogenicity results obtained for Lot A and the implications of this for its use as the reference standard for the potency assay*.

Lot A was used in a clinical Study, V72_41, designed to assess the consistency of the immune response between two lots of Bexsero with OMV manufactured at two different sites. Equivalence of the lots is demonstrated for all four vaccine antigens. However, despite the good reproducibility of the serum bactericidal assay, a certain degree of variability is expected considering a variety of factors, not the least the exogenous human complement source. Lot A has not been used in other clinical studies, however "Lot B", used as a comparator in this study, had also been used previously in other studies conducted in infants, toddlers and children (V72P6E1, V72P9E1, V72P12E1 and V72P13E2). Of note, regardless of the study and of the age population the lower limit of the 2-sided 95% CI for the percentages of subject with hSBA ≥1:4/1:5 for strain NZ98/254 after primary vaccination in these studies was higher than that observed in Study V72_41 (range: from 74% to 96% versus 72%). Therefore the immunogenicity results to this strain for both vaccine lots as measured in this study were in the low range and as a consequence Novartis concludes that the results observed with Lot A would also be lower than what would be generally expected. Finally, please note that in a multicomponent vaccine, such as Bexsero, the response to a single vaccine antigen is not the sole predictor of protection as antibodies to multiple antigens may act synergistically to enhance the vaccine's protective activity.

During development of the potency assay, a number of selected batches were used in a preapproved investigational plan in order to gain more information about the immunogenicity of the older clinical lots compared to the current reference standard (Lot A, manufactured in 2010) and commercial batches. The clinical batches tested were "Clinical Lots", manufactured in 2007. The assays were performed using 2 groups of 8 mice allocated in two different cages per dose level performed in one immunisation session. For both repetitions of the assay, the CI for the relative potency values for the OMV antigen included 1.0. This is the expected result if the samples are of equivalent potency. In addition, an analysis of the individual mouse titers for each of the three lots at all 6 dose levels demonstrates a similar response. Based on these results, Novartis concludes that the OMV in Lot A generates a comparable immune response in mice when compared to the Clinical Lots. It is recognised that there is potential for some degradation of potency over time but, when tested in 2012, the three lots demonstrated again comparable immune responses in mice.

In conclusion, although the immunogenicity results obtained for strain NZ98/254 for Lot A were lower than expected, overall clinical study results showed that subjects vaccinated with Lot A had an acceptable protective immune response against *N. meningitidis* serogroup B strains for the Bexsero antigens and Novartis considers Lot A as clinically qualified. In addition, the good physico-chemical comparability of Lot A with older lots used in the clinic supports the choice of using it as a reference standard for the potency assay.

Currently, due to its expiration, Novartis has changed from reference Lot A to "Lot C". The new reference standard was extensively tested during the validation of the *in vivo* assay. Results from assay validation have been used as part of the qualification of the new reference standard. Potency values for each of the four antigens were assigned to Lot C using Lot A as a comparator and based on the confidence interval. Novartis would like to confirm that the qualification of Lot C as the new reference standard is done based on physico-chemical characterisation (pre-approved protocol provided to TGA). Nonetheless,

Novartis is using Lot C in Study V72P12E2 in order to confirm the expected immune response in naive 4 years of age children. Results from this study are expected to be available by the end of 2013.

Concluding remarks

As noted by the Delegate, the impacts of invasive meningococcal disease are significant and the public health benefits of having a vaccine available would be invaluable. Novartis is of the view that, given (a) the comprehensive information about the risks and management of fever and its sequelae included in the proposed education program; (b) the commitment to implement under the Australian RMP appropriate risk minimisation activities; and (c) the commitment to provide the TGA with stability data for 5 recently produced commercial batches, starting with the T=6 months timepoint expected to be available in Q4 2013 and to notify the TGA of any results that could indicate a trend towards diminished potency over the 24-month storage period; there should be no objection to the approval of Bexsero for the active immunisation against invasive disease caused by *N. meningitidis* serogroup B strains in individuals from 2 months of age and older, regardless of the preferred dosing schedule in the 2 to 5 month age group.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Bexsero (*Neisseria meningitidis* Group B Neisseria Heparin Binding Antigen fusion protein (rbe) / Neisseria meningitidis Group B Neisseria Adhesin A protein (rbe) / Neisseria meningitidis Group B Factor H Binding Protein fusion protein (rbe) / Neisseria meningitidis serogroup B outer membrane vesicles) to have an overall positive benefit–risk profile for the proposed indication;

> *Bexsero is indicated for active immunisation of individuals from 2 months of age and older against invasive disease caused by Neisseria meningitidies group B strains*
>
> *This indication is based on short term immune responses*
>
> *The use of Bexsero should be in accordance with official recommendations*

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- The submission of results of ongoing studies as soon as practicable.

Proposed PI/CMI amendments:

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- Statement in the *Precautions* section of the PI and relevant sections of the CMI to accurately reflect the comprehensive information about the risks and management of fever and its sequelae.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Bexsero multi-component Meningococcal B vaccine (recombinant, adsorbed) suspension for injection 0.5 mL pre-filled syringe. The approved indication for these therapeutic goods is:

> *Bexsero is indicated for active immunisation against invasive disease caused by N. meningitidis group B strains. See PHARMACOLOGY for information on protection against specific group B strains.*
>
> *Bexsero is indicated for vaccination of individuals from 2 months of age and older.*

Specific conditions applying to these therapeutic goods:

- **Post marketing activities**

  The Bexsero (multi-component Meningococcal B vaccine) RMP, Version 4 (dated 12 November 2012) DLP 1 September 2012 with ASA Version 1.1 (dated 6 May 2013), included with submission PM-2012-02486-3-2, and any subsequent future revisions, as agreed with the TGA will be implemented in Australia. Also prior to product launch, the Health Care Professional Booklet (Version 1, dated 1 August 2013) and Patient Leaflet (Version 1, dated 31 July 2013) are to be incorporated into the RMP.

  Additional RMP and other post market requirements are those applicable generally to most new chemical entities.

  Other specific conditions for this product are:

  The sponsor is to update the TGA of the progress of the implementation of the pharmacovigilance plan no later than 6 months from the date of the approval letter. If the proposed studies do not commence within 6 months of approval a contingency pharmacovigilance plan is to be provided to and agreed with the TGA (The additional pharmacovigilance activities are entirely dependent the inclusion of Bexsero into a National Immunisation Program . Currently the location and commencement of these studies remains hypothetical).

  The sponsor is to submit to the TGA the results of currently ongoing clinical studies as soon as practicable after completion.

- **Batch release testing:**

  It is a condition of registration that all independent batches of Bexsero Multi-component Meningococcal B vaccine (recombinant, adsorbed) suspension for injection 0.5 mL pre-filled syringe imported into Australia are not released for sale until samples and the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

- **Lot release:**

  For each batch of vaccine imported into Australia the Sponsor should supply the following:

  - Complete summary protocols for manufacture and Quality Control, including all steps in production.
  - Number of doses to be released in Australia from each shipment.
  - Evidence of maintenance of satisfactory transport conditions between the manufacturer and Australia, such as graphs of temperature recordings, and a statement that the approved storage conditions have been met.
  - At least 20 doses of each first consignment of product lot with the Australian approved labels, PI and packaging. 3 doses of any further consignment of already

released product (including diluents) with the Australian approved labels, PI and packaging.

- Certificate of Release from the regulatory agency acting for the country of origin (OMCL).
- Any reagents, reference material and standards required to undertake testing, as requested by OLSS.

Distribution of each shipment of each batch of vaccine is conditional upon fulfilment of these conditions and receipt of a letter from the OLSS allowing release. Arrangement for delivery of the requested items will be provided.

- **Additional conditions recommended by the quality evaluator**

Novartis is to provide, at the earliest opportunity, finished product stability data for the 5 recently produced commercial batches of Bexsero currently on Stability testing (referred to in correspondence dated April 2013), starting with the T= 6 months time point followed by updates of the results at each testing time-point until the data package is considered adequate. Data on these batches of Bexsero should include identification and manufacturing dates of the drug substance lots used in their formulation.

Before release of the first batch of Bexsero onto the Australian market, the sponsor should provide TGA with:

- results of testing of three commercial batches of Bexsero tested at Release to the current finished product specifications (i.e. including Modified LAL, potency & Visible Particles) and evidence of release by the regulatory agency acting for the country of origin (OMCL).
- an assurance that the reference standard used in Immunogenicity testing of the batch has been appropriately clinically qualified.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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