Helping protect against Meningococcal B - A new vaccine for New Zealand

A/Prof Michael Nissen
Director, Scientific Affairs and Public Health
GSK Vaccines
Intercontinental Region
GlaxoSmithKline (GSK) can only recommend the use of treatments in accordance with the approved Data Sheet.

Please review the Data Sheet before prescribing. The Bexsero Data Sheet is available at: http://www.medsafe.govt.nz/profs/Datasheet/datasheet.htm
Invasive Meningococcal Disease (IMD)
Invasive Meningococcal Disease (IMD) causes significant morbidity and mortality

• Significant morbidity and mortality despite early diagnosis and appropriate medical treatment

• ~10% of cases are fatal\(^1,2\)

• Up to \textbf{1 in 5 survivors} of IMD (all serogroups) have \textit{permanent sequelae}\(^1,2\)

• Child survivors may experience major sequelae, including limb amputations, seizures and hearing loss\(^3\)

• More than 30% of child survivors experience other deficits such as psychological disorders, deficits of memory, digit amputations and unilateral hearing loss\(^3\)


IMD = invasive meningococcal disease VPDs = vaccine preventable diseases
Early misdiagnosis is common
Medical intervention often does not occur until late

**13-24 HOURS**

POTENTIALLY LETHAL
Most progressed from non-specific initial symptoms to close to death within 24 hours

~13 hours - Median time to first hospitalisation*

- Neck pain and stiffness
- Hemorrhagic rash
- Floppy muscle tone#
- Bulging fontanelle*
- Photophobia
- Confusion and delirium^*
- Seizure
- Loss of consciousness

* in infants <1 year
# in children <5 years
^ in children >1 year

**0-7 HOURS**

NON SPECIFIC SYMPTOMS

- Fever
- Irritability
- Nausea or vomiting
- Poor appetite or feeding
- Drowsiness
- Headache^*
- Sore throat
- Thirst
- Leg pain
- General aches

* in children >1 year

**8-12 HOURS**

~8 hrs - Median time to first GP consultation*

- Cold hands and feet
- Abnormal skin colour
- Breathing difficulty
- Increased thirst
- Diarrhoea

* in infants <1 year

Meningococcal disease is caused by the bacterium Neisseria meningitidis\textsuperscript{1}

- Meningococci are classified into serogroups, determined by the components of the polysaccharide capsule\textsuperscript{1}

- Globally, 6 serogroups most commonly cause disease\textsuperscript{2}

- In New Zealand, serotypes B and C cause the majority of IMD\textsuperscript{3}. In 2016, 70% of meningococcal cases that could be typed were group B

Transmission & Infection

**N. meningitidis** is transmitted via aerosol droplets or through direct contact

- From person to person through contact with respiratory or throat secretions from an infected person\(^1\)

- Close and prolonged contact facilitates the spread of the disease, e.g. kissing, sneezing or coughing on someone, living in close quarters (dormitory, sharing eating or drinking utensils)\(^2\)

- The bacterium attach to the surface of the nasopharynx and multiply\(^3\)
  - This can lead to **transient carriage** (asymptomatic) or result in **invasive disease**

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Meningococcal Disease in New Zealand
NZ has a high rate of IMD compared with other countries worldwide*

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Notification rate</th>
<th>Source</th>
</tr>
</thead>
</table>

*Some countries have an IMD vaccination programme in place*
IMD incidence in NZ is unpredictable and can change rapidly

Figure 22. Meningococcal disease notifications by year, 1989–2016

1. ESR Notifiable Diseases in New Zealand Annual Report:
Serogroup B causes the majority of IMD in New Zealand

IMD strain distribution by year 2007-2017 in New Zealand, lab-confirmed cases

In 2016, 70% of meningococcal cases that could be typed were serogroup B

1. The Institute of Environmental Science and Research, Meningococcal disease epidemiology data request. GSK. 2018.
IMD disproportionately affects the <1 age group in NZ

Rate per 100,000 of total IMD and Meningococcal B disease in New Zealand in 2016

Infants have the highest IMD notification rate of 18.6 per 100,000

1. The Institute of Environmental Science and Research, Meningococcal disease epidemiology data request. GSK. 2017.
Infants <1 year are most vulnerable to meningococcal infection

Infants < 1 year have the highest notification rate of invasive meningococcal disease, over 10 times the national average in 2016.1

Meningococcal B is the most common cause of IMD in infants < 1 year.2

While the case fatality rate is highest in older populations (>60 years), infants (<1 year) and young children (1-4 years) experience the highest rates of complications.3,4

2. The Institute of Environmental Science and Research, Meningococcal disease epidemiology data request. GSK. 2017.
Māori and Pacific Island populations are disproportionately impacted by Meningococcal B disease in NZ.

Average Meningococcal B notification rate 2007-2016

Māori and Pacific <1 year olds have approx. 6 times higher Meningococcal B rates¹

1. The Institute of Environmental Science and Research, Meningococcal disease epidemiology data request. GSK. 2017.
Bexsero (4CMenB) - Vaccine Development
Multicomponent Meningococcal group B Vaccine (recombinant, adsorbed)
A capsular vaccine for Meningococcal B?

Vaccines with a single subcapsular antigen component do not offer broad protection against Meningococcal B disease

### Capsular vaccines

- Poorly immunogenic\(^1\),\(^2\)
  - Structural homology between the B polysaccharide of the capsule and human tissue\(^1\),\(^2\)

![N meningitidis bacterial capsule](image)

*Image from Nassif et al. 2002\(^3\)*

### Outer membrane vesicle (OMV) vaccines

- Immunogenic and proven effective for a **single** homologous serogroup B strain\(^4\),\(^5\)
- Limited protection against heterologous meningococcal serogroup B strains\(^4\),\(^5\)
  - Serogroup B strains are highly diverse\(^4\),\(^5\)
    - >5000 sequence types identified\(^6\)
    - >600 PorA variants (the dominant antigen in OMV)\(^4\)

![Outer membrane “blebs” of N meningitidis](image)

*Image from Devoe et al. 1973\(^7\)*

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Bexsero contains 4 antigenic components
Identified using a “reverse vaccinology” approach

**fHbp: factor H-binding protein**
- Binds factor H, which enables bacterial survival in the blood\(^1,2\)

**NadA: neisserial adhesin A**
- Promotes adherence to and invasion of human epithelial cells\(^3\)–\(^5\)
- May be important for colonisation\(^4\)

**NHBA: neisseria heparin-binding antigen**
- Binds heparin, which may promote bacterial survival in the blood\(^6\)
- Present in virtually all strains\(^6,7\)

**NZ PorA P1.4: porin A**
- Major OMV protein\(^8\)
- Shown to induce strain-specific bactericidal response when used in MeNZB OMV vaccine\(^^8\)

[^Developed by Chiron Vaccines in association with the Norwegian Institute of Public Health. OMV, outer membrane vesicle.]

Multiple antigens may provide synergistic killing, improve strain coverage, and insure against mutations\(^9,10\)

Clinical trial experience with Bexsero
Studies included subjects from 2 months of age

Bexsero safety was evaluated in 13 studies including 9 randomised controlled clinical trials

Infants and children 2 months to <2 years of age
- 5849 received at least 1 dose of Bexsero
- 3285 received booster dose in second year of life

250 children 2 to 10 years of age

2677 adolescents (≥11 years of age) and adults

8776 subjects received at least 1 dose of the vaccine.

Bexsero is indicated for active immunisation against invasive disease caused by N. meningitidis group B strains.

Bexsero is indicated for vaccination of individuals from 2 months of age and older. The use of Bexsero should be in accordance with official recommendations.

Dosing schedules for Bexsero in New Zealand

Administer by deep intramuscular injection, preferably in the anterolateral aspect of the thigh in infants or in the deltoid muscle region of the upper arm in older subjects.

<table>
<thead>
<tr>
<th>Dosage:</th>
<th>Primary immunisation</th>
<th>Minimum interval between primary doses</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants 2-5 months*</td>
<td>3 doses</td>
<td>≥ 1 month</td>
<td>Second year of life**</td>
</tr>
<tr>
<td>Infants 6-11 months</td>
<td>2 doses</td>
<td>≥ 2 months</td>
<td>Second year of life#</td>
</tr>
<tr>
<td>Toddlers and children 12 months-10 years</td>
<td>2 doses</td>
<td>≥ 2 months</td>
<td>Need not established</td>
</tr>
<tr>
<td>Adolescents &amp; Adults 11-50 years^</td>
<td>2 doses</td>
<td>≥ 1 month</td>
<td></td>
</tr>
</tbody>
</table>

*The safety and efficacy of the vaccine in infants <8 weeks has not yet been established. No data available

# ≥2 months post primary series

** ≥6 months post primary series

^No data available in individuals above 50 years of age

Bexsero real world effectiveness data
Bexsero approvals and recommendations

Summary (as of April 2018)

39 APPROVALS

• EU/EEA: 31 countries (plus Andorra)*
• Other: Argentina², Australia³, Brazil⁴, Canada⁵, Chile⁶, Uruguay⁷, USA⁸

19 CLINICAL RECOMMENDATIONS†

• Australia⁹, Austria¹⁰, Belgium¹¹, Brazil¹², Canada¹³, Cyprus¹⁴, Czech Republic¹⁵, France¹⁶, Germany¹⁷, Greece¹⁸, Hungary¹⁹, Poland²⁰, Portugal²¹, Spain²²
• Andorra²³, Ireland²⁴, Italy²⁵, UK²⁶, USA²⁷ (see below)

6 NIPs

• Andorra²³, Ireland²⁴, Italy²⁵, Lithuania, UK²⁶: NIPs implemented
• USA: Category B national recommendation²⁷

NIPs, National Immunisation Programmes
* BEXSERO approved across EU and EEA countries under a centralised procedure (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, UK; Andorra is not listed in EU SmPC, but follows the same approvals as Spain)
† Clinical recommendation in countries where BEXSERO has been approved

Please refer to slide notes for references
Real world experience with Bexsero

UK: National MenB vaccination programme

In 2015, universal Meningococcal B infant vaccination was introduced to help protect against Meningococcal B disease in the UK (~700,000 infants per year were targeted for vaccination)

Canada: Regional vaccination campaign in Quebec and University outbreak in Nova Scotia

Regional campaign in Saguenay-Lac-Saint-Jean, Quebec

In 2014, 57,038 residents or those in education aged ≥2 months to ≤20 years were targeted for Meningococcal B vaccination to help protect against the high incidence of disease in the region. Between 5 May and 17 June 2014, 43,740 individuals received the first dose of vaccine.

Outbreak at Acadia University, Nova Scotia

In 2015, a two-dose Meningococcal B vaccination campaign was introduced at Acadia University, Nova Scotia – 2967 individuals received the first dose in February to March 2015 and 987 participants were assessed in an online safety survey following the first dose.

USA: University outbreaks

Princeton University and University of California at Santa Barbara

In 2013, the FDA authorised vaccination campaigns in response to two university outbreaks; surveillance data for 15,236 individuals vaccinated with Bexsero have been reported.

Santa Clara

In 2016, a two-dose vaccination campaign was introduced – 4921 individuals received the first dose in February 2016.

*Under IND protocol prior to US approval (January 2015)

IND, investigational new drug

Bexsero use in infants less than 6 months of age

Immunogenicity and co-administration
Dosage and Administration

Administer by **deep intramuscular injection**, preferably in the anterolateral aspect of the thigh in infants.

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*The safety and efficacy of the vaccine in infants <8 weeks has not yet been established. No data available.

Bexsero can be co-administered with routine childhood vaccinations

Bexsero can be given concomitantly with any of the following vaccine antigens, either as monovalent or as combination vaccines

<table>
<thead>
<tr>
<th>Diphtheria</th>
<th>Pneumococcal conjugate (7-valent)</th>
<th>Measles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus</td>
<td></td>
<td>Mumps</td>
</tr>
<tr>
<td>Acellular pertussis</td>
<td></td>
<td>Rubella</td>
</tr>
<tr>
<td>Inactivated poliomyelitis</td>
<td></td>
<td>Varicella</td>
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<tr>
<td>Hepatitis B</td>
<td></td>
<td></td>
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<tr>
<td>Haemophilus influenzae type b</td>
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</tbody>
</table>

- **No clinically significant interference** in immune response for either Bexsero or the concomitantly administered vaccines
- There is a more frequent occurrence of fever, tenderness at the injection site, change in eating habits and irritability when Bexsero is co-administered with other vaccines
- When given at the same time as other vaccines, Bexsero should be given at separate injection sites

Bexsero use in infants less than 6 months of age

Safety and use of paracetamol
Bexsero was well tolerated in infants

Bexsero tolerability compared to routine vaccines (PCV7 and DTPa-IPV-HBV/Hib)

Results post dose 1: Local reactions (reported in the 7 days post vaccination)

- There was no increase in the incidence or severity of the adverse reactions with subsequent doses of the vaccination series\(^1\)

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* Bexsero alone, N=626: infants vaccinated with BEXSERO at 2, 4 and 6 months separately from routine vaccines which were administered at 3, 5, and 7 months. Data shown are from the Bexsero time point only.

* Routine alone: N=310. Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib. Infants vaccinated at 2, 3 and 4 months

\(^1\) Pain was categorised as severe if subject cried when injected limb was moved or did not move injected limb. Erythema, induration and swelling were categorized as severe if local reaction was >100 mm.\(^1\)

\(^\ast\) Adapted from Gossger et al, 2012\(^1\)

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Bexsero was well tolerated in infants

For Bexsero when given alone or concomitantly with routine vaccinations, compared to routine vaccinations alone: Post dose 1

Legend

- Bexsero + routine*^ (2,4,6 months)
- Bexsero# (2,4,6 months)
- Routine*§ (2,3,4 months)
- Severe†
- Rash
- Fever ≥39°C

Adapted from Gossger et al, 2012

*Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib. ^Bexsero+Routine, N=624; #Bexsero alone, N=626: infants vaccinated with BEXSERO at 2, 4 and 6 months separately from routine vaccines which were administered at 3, 5, and 7 months. Data shown are from the Bexsero time point only; §Routine alone: N=310.

†Adverse events for systemic reactions defined as severe if: change in eating habits (child missed more than 2 feedings), sleepiness (child sleeps most of the time and is hard to arouse), vomiting (child has several vomiting episodes and cannot keep food down for prolonged time), diarrhea (child has more than 6 liquid stools, with no solid consistency), irritability (child is unable to be consoled), and unusual crying (unusual, high-pitched screaming, unlike the child’s normal crying, that persists for ≥3 hours).

Rash was categorized as any (shown) or urticarial; fever was categorized as axillary temperatures ≥38°C and ≥39°C.†

• There was no increase in the incidence or severity of the adverse reactions with subsequent doses of the vaccination series

Impact of prophylactic paracetamol on fever

When Bexsero was given concomitantly with routine infant vaccines at 2, 3 and 4 months of age (after any dose)

- Use of paracetamol resulted in a **significant reduction** in the incidence and severity of fever following administration of Bexsero without compromising vaccine immunogenicity¹

Prophylactic paracetamol had no clinically relevant impact on immunogenicity of routine vaccines

Bexsero given concomitantly with routine infant vaccines (2-3-4 month schedule)

*Routine: PCV7 and DTaP-HBV-IPV/Hib.
‡For initially seropositive subjects (baseline ≥ lower limit of quantification [LLQ]), maintenance of pre-vaccination levels; if baseline < LLQ (initially seronegative subjects), post-third dose ≥ LLQ.

This study was not powered for a noninferiority analysis.

Each vaccine group followed a 2-3-4 month accelerated schedule.
Blood draw at 5 months.

Bexsero safety, presentation and storage
Important safety considerations

Precautions

- Bexsero is not expected to provide protection against all circulating Meningococcal B strains
- No data in:
  - subjects above **50 years of age** or in patients with **chronic medical conditions**

  Although no natural rubber latex is detected in the syringe tip cap, the safe use of Bexsero in latex-sensitive individuals has not been established.

- Bexsero may contain Kanamycin (< 0.01 micrograms/dose; used in early manufacturing process but removed at later stages). Safe use of Bexsero in **kanamycin-sensitive individuals** has not been established

Please review New Zealand Data Sheet for further information

### Presentation and storage

**Presentation**

- 0.5mL suspension in a pre-filled syringe (needles not supplied)
- Upon storage of the suspension product, a fine off-white deposit may form. Shake the vaccine well before use.
- Visually inspect for particulate matter or discoloration.

**Shelf life**

- 3 years

**Storage**

- Store in a refrigerator (2-8°C)
- Do not Freeze
- Protect from light
Summary

- Invasive meningococcal disease is a rare, but potentially fatal disease.
- Serotypes B and C cause the majority of IMD in New Zealand.
  - In 2016, 70% of meningococcal cases that could be typed were group B.

- Bexsero is a multicomponent, meningococcal serogroup B, recombinant protein vaccine.
  - Induces production of bactericidal antibodies.
  - Vaccine immunogenicity and safety has been evaluated in 13 clinical trials.
  - Indicated for use in individuals ≥ 2 months of age or according to official recommendations.
  - Acceptable safety and tolerability profile.
  - Use of *prophylactic paracetamol* is recommended when administered to infants and children under 2 years of age.
Bexsero Prescribing Information

Bexsero® (Multicomponent Meningococcal group B Vaccine) is available as a private-purchase prescription medicine for active immunisation against invasive disease caused by N. meningitidis group B from 2 months of age. The use of Bexsero should be in accordance with official recommendations- a prescription charge will apply. A trained pharmacist can also administer Bexsero to a person aged 16 years and older. A single 0.5mL dose contains 50mcg of Neisseria meningitidis Group B Neisseria Heparin Binding Antigen fusion protein, 50mcg of Neisseria meningitidis Group B Neisseria Adhesin A protein, 50mcg of Neisseria meningitidis Group B Factor H Binding Protein fusion protein, 25 mcg of Outer membrane vesicles (OMV) from Neisseria meningitidis group B strain NZ98/254 measured as amount of total protein containing the PorA P1.4. Dosage and Administration: Administered by deep intramuscular injection. 0.5ml dose in a pre-filled syringe. Infants (2-5 months): 3 doses (≥1 month interval), booster dose at 12-23 months (≥6 month interval between primary series and booster). Unvaccinated infants (6-11 months): 2 doses (≥2 month interval), booster dose at 12-23 months (≥2 month interval between primary series and booster). Unvaccinated toddlers and children (12 months – 10 years): 2 doses (≥2 month interval), need for booster not established. 11-50 years: 2 doses (≥1 month interval), need for booster not established. Contraindications: Hypersensitivity to any vaccine component. Precautions: Bexsero should never be administered intravenously, subcutaneously or intradermally. Postpone vaccination during acute severe febrile illness. Anticipate psychogenic response (syncope, hyperventilation). Manage fever (prophylactic antipyretics). Individuals with impaired immune responsiveness. No data for use in subjects aged ≥50 years or patients with chronic medical conditions. Apnoea in very premature infants. Kanamycin-sensitive individuals. Pregnancy (category B1). Lactation. May contain latex. As with any vaccine, vaccination with Bexsero may not protect all vaccine recipients. Bexsero is not expected to provide protection against all circulating meningococcal group B strains. Bexsero should be administered at separate injection sites. Adverse reactions: Infants & Toddlers: eating disorders, sleepiness, unusual crying, diarrhoea, vomiting, rash, fever (≥39.5°C), injection site reactions, irritability, arthralgia. Adolescents & Adults: headache, nausea, injection site reactions, malaise, myalagia, arthralgia. This is not a full list. Before prescribing Bexsero, please review the full Data Sheet at www.medsafe.govt.nz. Bexsero is a registered trade mark of the GlaxoSmithKline group of companies. Marketed by GlaxoSmithKline NZ Ltd, Auckland.

Adverse events involving GlaxoSmithKline products should be reported to GSK Medical Information on 0800 808 500.