

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

BEXSERO Multicomponent Meningococcal group B Vaccine (recombinant, adsorbed)
0.5 mL suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 mL) of BEXSERO contains:

Neisseria meningitidis Group B Neisseria Heparin Binding Antigen fusion protein^{1,2} (rbe) - 50 micrograms

Neisseria meningitidis Group B Neisseria Adhesin A protein^{1,2} (rbe) - 50 micrograms

Neisseria meningitidis Group B Factor H Binding Protein fusion protein^{1,2} (rbe) - 50 micrograms

Outer membrane vesicles (OMV) from *Neisseria meningitidis* group B strain NZ98/254 measured as amount of total protein containing the PorA P1.4² - 25 micrograms

¹Produced in *E. coli* cells by recombinant DNA technology. The NHBA (Neisseria Heparin Binding Antigen) is derived from strain NZ98/254 and is fused with accessory protein 953, derived from strain 2996; NadA (Neisseria adhesin A) is derived from strain 2996; fHBP (factor H Binding Protein) is derived from strain MC58 and is fused with accessory protein 936, derived from strain 2996.

²Adsorbed on aluminium hydroxide (0.5 mg Al³⁺).

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Suspension for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BEXSERO is indicated for active immunisation against invasive disease caused by *N. meningitidis* group B strains. See section 5.1 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.

4.2 Dose and method of administration

Dose

In the absence of compatibility studies, this medicinal product must not be mixed with

other medicinal products. BEXSERO can be given at the same time as other immunisations, provided that the vaccine is administered either at a different site or away from the injection site of the other vaccine, according to local guidelines.

Infants 2 months to 5 months of age at time of first dose

The primary infant vaccination schedule consists of two or three doses, each of 0.5 mL, with an interval of not less than 2 months between doses (2-dose primary schedule) or 1 month between doses (3-dose primary schedule). The first dose should be given no earlier than 2 months of age. The safety and efficacy of BEXSERO in infants less than 8 weeks of age has not yet been established. No data are available. A booster dose is recommended in the second year of life, from the age of 12 months or later, with an interval of at least 6 months between the primary series and booster dose (see section 5.1 Pharmacodynamic properties).

Infants 6 months to 11 months of age at the time of the first dose

The vaccination schedule consists of two doses, each of 0.5 mL, with an interval of not less than 2 months between doses. A booster dose is recommended in the second year of life with an interval of at least 2 months between the primary series and booster dose. (see section 5.1 Pharmacodynamic properties).

Toddlers 12 months to 23 months of age at the time of the first dose

The vaccination schedule consists of two doses, each of 0.5 mL, with an interval of not less than 2 months between doses. The need for a booster dose after this vaccination schedule has not been established (see section 5.1 Pharmacodynamic properties).

Children 2 years to 10 years of age at the time of the first dose

The vaccination schedule consists of two doses, each of 0.5 mL, with an interval of not less than 1 month between doses. The need for a booster dose after this vaccination schedule has not been established (see section 5.1 Pharmacodynamic properties).

Adolescents and adults from 11 years of age at the time of the first dose

Two doses, each of 0.5 mL, with an interval of not less than 1 month between doses. The need for a booster dose after this vaccination schedule has not been established (see section 5.1 Pharmacodynamic properties).

The safety and efficacy of BEXSERO in individuals above 50 years of age have not been established.

Table 1: Summary of Dosages

Age at first dose	Primary Immunisation	Intervals between Primary Doses	Booster
Infants, 2 months to 5 months ^a	Two doses each of 0.5 mL	Not less than 2 months	Yes, 1 dose in the second year of life, from the age of 12 months or later, with an interval of at least 6 months between the primary series and booster dose ^b
	Three doses each of 0.5 mL	Not less than 1 month	
Infants, 6 months to 11 months	Two doses each of 0.5 mL	Not less than 2 months	Yes, 1 dose in the second year of life with an interval of at least 2 months between the primary series and booster dose ^b
Toddlers, 12 months to 23 months	Two doses each of 0.5 mL	Not less than 2 months	Need not established ^b
Children, 2 years to 10 years	Two doses each of 0.5 mL	Not less than 1 months	Need not established ^b
Adolescents (from, 11 years) and adults*	Two doses each of 0.5 mL	Not less than 1 month	Need not established ^b

^a The first dose should be given no earlier than 2 months of age. The safety and efficacy of BEXSERO in infants less than 8 weeks of age has not yet been established. No data are available.

^b see section 5.1 Pharmacodynamic properties

* The safety and efficacy of BEXSERO in individuals above 50 years of age have not been established.

Sufficient data are not available on the safety and effectiveness of using BEXSERO and other meningococcal group B vaccines interchangeably to complete the vaccination series. Therefore, it is recommended that subjects who receive a first dose of BEXSERO complete the vaccination course with BEXSERO.

Method of administration

The vaccine is given 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.

Separate injection sites must be used if more than one vaccine is administered at the same time. Administer in accordance with local guidelines.

The vaccine must not be injected intravenously, subcutaneously or intradermally and must not be mixed with other vaccines in the same syringe.

BEXSERO is for single use in one patient only.

For instructions on the handling of the vaccine before administration, see section 6.6 Special precautions for disposal and other handling.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients, see section 6.1 List of excipients

4.4 Special warnings and precautions for use

As with other vaccines, administration of BEXSERO should be postponed in subjects suffering from an acute severe febrile illness. However, the presence of a minor infection, such as cold, should not result in the deferral of vaccination.

Do not inject intravascularly, subcutaneously or intradermally.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection (see section 4.8 Undesirable effects). It is important that procedures are in place to avoid injury from fainting.

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 (see section 5.1 Pharmacodynamic effects).

As with many vaccines, health care professionals should be aware that a temperature elevation may occur following vaccination of infants and toddlers. Accordingly, patients and/or their care givers should be made aware of the risks and management of fever and its sequelae. In infant study V72P13, fever $\geq 38.0^{\circ}\text{C}$ was reported by 78%, 84% and 73% of participants after dose 1, 2 and 3, respectively, in the BEXSERO vaccine group, compared with 44%, 59% and 50% of participants receiving the routine vaccines alone. In the same study, fever $\geq 39.5^{\circ}\text{C}$ was reported by 5%, 7% and 4% of participants after dose 1, 2 and 3, respectively, in the BEXSERO vaccine group, compared with 1%, 1% and 2% of participants 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.

Individuals with impaired immune responsiveness, whether due to the use of immune-suppressive therapy, a genetic disorder, or other causes, may have reduced antibody response to active immunisation. Immunogenicity data are available in individuals with complement deficiencies, asplenia, or splenic dysfunction (see section 5.1 Pharmacodynamic effects).

Individuals receiving treatment that inhibits terminal complement activation (for example, eculizumab) remain at increased risk of invasive disease caused by *Neisseria meningitidis* group B even following vaccination with BEXSERO.

The safety and efficacy of BEXSERO in individuals above 50 years of age have not been established. There are limited data in patients with chronic medical conditions.

The potential risk of apnoea and the need for respiratory monitoring for 48-72 hours should be considered when administering the primary immunisation series to very premature infants (born \leq 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

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.

Kanamycin is used in early manufacturing process and is removed during the later stages of manufacture. If present, kanamycin levels in the final vaccine are less than 0.01 micrograms per dose. The safe use of BEXSERO in kanamycin-sensitive individuals has not been established.

4.5 Interaction with other medicines and other forms of interaction

BEXSERO can be given concomitantly with any of the following vaccine antigens, either as monovalent or as combination vaccines: diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, hepatitis B, heptavalent pneumococcal conjugate, measles, mumps, rubella, varicella, and meningococcal group C-CRM conjugate.

Clinical studies demonstrated that the immune responses of the co-administered routine vaccines were unaffected by concomitant administration of BEXSERO. Inconsistent results were seen across studies for responses to inactivated poliovirus type 2 and pneumococcal conjugate serotype 6B, but these data do not suggest clinically significant interference.

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 (as per local guidelines) 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.

Concomitant administration of BEXSERO with vaccines other than those mentioned above has not been studied. Administration of vaccines containing whole cell pertussis concomitantly with BEXSERO has not been studied and thus is not recommended.

When given concomitantly with other vaccines BEXSERO must be administered at separate injection sites (see section 4.2 Dose and method of administration).

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B1.

Insufficient clinical data on exposed pregnancies are available.

The potential risk for pregnant women is unknown. Nevertheless, vaccination should not be withheld when there is a clear risk of exposure to meningococcal infection.

A reproductive and developmental toxicity study has been performed in female rabbits intramuscularly injected 35, 21, and 7 days prior to mating and on gestation days 7 and 20 with the clinical dose of BEXSERO (approximately 10 times the human dose based on body weights). There was no evidence of maternal, foetal, or postnatal developmental effects due to BEXSERO. Vaccine-specific antibodies were detected in rabbit foetuses and kits.

Breast-feeding

Information on the safety of the vaccine to women and their children during breast-feeding is not available. The benefit-risk ratio must be examined before making the decision to immunise during breast-feeding.

No adverse reactions were seen in vaccinated maternal rabbits or in their offspring through day 29 of lactation. BEXSERO was immunogenic in maternal animals vaccinated prior to lactation, and vaccine-specific antibodies were detected in the offspring, but antibody levels in milk were not determined.

Fertility

There are no data on fertility in humans.

There were no effects on the mating performance or fertility of female rabbits in a reproductive and developmental toxicity study in which rabbits were intramuscularly injected with the clinical dose of BEXSERO 35, 21, and 7 days prior to mating and on gestation days 7 and 20. Male fertility has not been assessed in animals.

4.7 Effects on ability to drive and use machines

BEXSERO has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 Undesirable effects, may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of BEXSERO was evaluated in 13 studies including 9 randomised controlled clinical trials with 7802 participants (from 2 months of age) who received at least one dose of BEXSERO and in a subsequent study in 974 young adults. Among BEXSERO recipients, 5849 were infants and toddlers (less than 2 years of age), 250 were children (2 to 10 years of age) and 2677 were adolescents and adults. Of the participants who received a primary infant series of BEXSERO, 3285 received a booster dose in the second year of life. Data for 988 infants and children (less than 2 years of age) and 801 children (2 to 10 years of age) exposed to BEXSERO in subsequent studies have additionally been evaluated.

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.

In clinical studies in infants, fever occurred more frequently when BEXSERO was co-administered with routine vaccines (containing the following antigens: pneumococcal 7-valent conjugate, diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis and *Haemophilus influenzae* type b) than when it was given alone. Higher rates of antipyretic use were also reported for infants vaccinated with BEXSERO and routine vaccines. When BEXSERO was given alone, the frequency of fever was similar to that associated with routine infant vaccines administered during clinical trials. When fever occurred, it generally followed a predictable pattern, with the majority resolving by the day after vaccination.

In adolescents and adults the most common local and systemic adverse reactions observed were pain at the injection site, malaise and headache.

No increase in the incidence or severity of the adverse reactions was seen with subsequent doses of the vaccination series.

List of adverse reactions

Adverse reactions (following primary immunisation or booster dose) considered as being at least possibly related to vaccination have been categorised by frequency.

Frequencies are defined as follows:

Very common:	($\geq 1/10$)
Common:	($\geq 1/100$ to $< 1/10$)
Uncommon:	($\geq 1/1,000$ to $< 1/100$)
Rare:	($\geq 1/10,000$ to $< 1/1,000$)
Very rare:	($< 1/10,000$)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infants, Toddlers, and Children (up to 10 years of age)

Metabolism and nutrition disorders

Very common: eating disorders

Nervous system disorders

Very common: sleepiness, unusual crying, headache

Uncommon: seizures (including febrile seizures)

Vascular disorders

Uncommon: pallor (rare after booster)

Rare: Kawasaki syndrome

Gastrointestinal disorders

Very common: diarrhoea, vomiting (uncommon after booster)

Skin and subcutaneous tissue disorders

Very common: rash (toddlers) (uncommon after booster)

Common: rash (infants and children 2 to 10 years of age)

Uncommon: eczema

Rare: urticaria

General disorders and administration site conditions

Very common: fever ($\geq 38^\circ\text{C}$), injection site tenderness (including severe injection site tenderness defined as crying when injected limb is moved), injection site erythema, injection site swelling, injection site induration, irritability

Common: fever ($\geq 39.5^\circ\text{C}$)

Uncommon: fever ($\geq 40^\circ\text{C}$)

Musculoskeletal and connective tissue disorders

Very common: arthralgia

Adolescents (from 11 years of age) and Adults

Nervous system disorders

Very common: headache

Gastrointestinal disorders

Very common: nausea

General disorders and administration site conditions

Very common: injection site pain (including severe injection site pain defined as unable to perform normal daily activity), injection site swelling, injection site induration, injection site erythema, malaise

Musculoskeletal and connective tissue disorders

Very common: myalgia, arthralgia

Adverse reactions from post-marketing spontaneous reports

In addition to reports in clinical trials, worldwide voluntary reports of adverse reactions received for BEXSERO since market introduction are listed below. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

General disorders and administration site conditions

Fever (adolescents from 11 years of age and adults)

Injection site reactions (including extensive swelling of the vaccinated limb, blisters at or around the injection site and injection site nodule which may persist for more than one month)

Immune system disorders

Allergic reactions (including anaphylactic reactions)

Nervous system disorders

Hypotonic-hyporesponsive episode

Syncope or vasovagal responses to injection

Skin and subcutaneous tissue disorders

Rash (adolescents from 11 years of age and adults)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via:

<https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Experience of overdose is limited. In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: meningococcal vaccines, ATC code: J07AH09

Mechanism of action

Immunisation with BEXSERO is intended to stimulate the production of bactericidal antibodies against the vaccine antigens (NHBA, NadA, fHBP, and PorA P1.4 (the immunodominant antigen present in the OMV component)). The resultant antibodies are expected to be protective against Invasive Meningococcal Disease (IMD). As these antigens are variably expressed by different strains, meningococci that express these antigens at sufficient levels are susceptible to killing by vaccine-elicited antibodies. The vaccine antigens present in BEXSERO are also expressed by strains belonging to meningococcal groups other than group B. Limited data suggest protection against some non-group B strains, however, the extent is not yet determined.

Clinical efficacy and safety

The efficacy of BEXSERO has been inferred by measuring bactericidal antibody responses to each of the vaccine antigens NadA, fHBP, NHBA and PorA P1.4, using a set of four meningococcal group B reference strains (5/99, H44/76, M10713 and NZ98/254). Bactericidal antibodies against these strains were measured by the Serum Bactericidal Assay using human serum as the source of complement (hSBA). Strain H44/76 measured bactericidal antibody directed against fHBP; strain 5/99 measured bactericidal antibody directed against NadA; strain M10713 measured bactericidal antibody directed against NHBA; and strain NZ98/254 measured bactericidal antibody directed against PorA P1.4 in the OMV vaccine component. Data are not available from all vaccine schedules using strain M10713.

Immunogenicity

The primary immunogenicity endpoint was measured as the proportion of participants with hSBA equal to or above the threshold of 1:4 against each of the meningococcal group B reference strains. This threshold, used in early-stage clinical studies (V72P6, V72P9, V72P4, V72P5 and V72P10), is an accepted correlate of protection. Based on the intermediate precision of the validated assay a threshold of 1:5 was then set to ensure 95% certainty of a true response of 1:4. This cut-off was used to define seropositive responses in late-stage clinical studies in infants and children (V72P13, V72P12, V72P12E1, V72P13E1, V72P16, V72P13E2, V72P6E1, V72P9E1, V72_28, V72_28E1 and V72P10E1). Immunogenicity was evaluated in randomised, multicentre, clinical trials that enrolled infants, children, adolescents and adults.

Immunogenicity in infants 2 months to 5 months of age

Three dose primary schedule followed by a booster

In infant studies V72P13, V72P12 and V72P16, participants received three doses of BEXSERO either at 2, 4 and 6 or 2, 3 and 4 months of age with concomitant routine vaccines and a booster dose in their second year of life, as early as 12 months of age. Control groups received only routine childhood vaccinations. Sera were obtained before vaccination, one month after the third vaccination (Table 2) and one month after booster vaccination (Table 3).

Across these studies, baseline geometric mean titres (GMTs) against all four reference strains were uniformly low ranging from 1.02 to 3.28 in the BEXSERO groups and 1.01 to 4.08 in the controls.

One month after the third BEXSERO vaccination, bactericidal responses against the meningococcal reference strains fHBP, NadA, PorA P1.4 and NHBA antigens were high for both schedules. For NHBA antigen, the bactericidal responses were higher in infants vaccinated at the 2,4,6-month schedule than for those vaccinated on the 2,3,4-month schedule. The clinical consequence of the reduced immunogenicity of the NHBA antigen following the 2, 3, 4-month schedule is not known. Following routine childhood vaccination in the control group the mean hSBA GMTs against meningococcal reference strains remained low ranging from 1.04 to 2.24.

Table 2: Serum bactericidal antibody responses at 1 month following the third dose of BEXSERO given at 2, 3, 4 (Studies V72P12, V72P16) or 2, 4, 6 (Study V72P13) months of age.

Antigen*	Response (95% CI)	Study V72P13 2, 4, 6 months	Study V72P12 2, 3, 4 months	Study V72P16 2, 3, 4 months
fHBP	% seropositive**	N=1149 100% (99-100)	N=273 99% (97-100)	N=170 100% (98-100)
	hSBA GMT***	91 (87-95)	82 (75-91)	101 (90-113)
NadA	% seropositive	N=1152 100% (99-100)	N=275 100% (99-100)	N=165 99% (97-100)
	hSBA GMT	635 (606-665)	325 (292-362)	396 (348-450)
PorA P1.4	% seropositive	N=1152 84% (82-86)	N=274 81% (76-86)	N=171 78% (71-84)
	hSBA GMT	14 (13-15)	11 (9.14-12)	10 (8.59-12)
NHBA	% seropositive	N=100 84% (75-91)	N=112 37% (28-46)	N=35 43% (26-61)
	hSBA GMT	16 (13-21)	3.24 (2.49-4.21)	3.29 (1.85-5.83)

* The following strains of group B meningococci, which were isolated from cases of invasive disease, were used to assess functional immunogenicity against each of the vaccine antigens by hSBA:

- fHBP antigen: strain 44/76

- NadA antigen: strain 5/99
- immunodominant PorA P1.4 component of OMV: strain NZ98/254
- NHBA antigen: strain M10713

** % seropositive = the percentage of participants who achieved an hSBA \geq 1:5.

*** GMT = geometric mean titre.

Table 3 summarises antibody persistence pre-booster dose 8 months after primary vaccination at 2, 3 and 4 months of age and at 6 months after vaccination at 2,4 and 6 months of age. Table 3 also summarises an antibody response for both regimens one month after a booster dose administered at 12 months of age, and antibody persistence 12 months after the booster dose for the 2,4 and 6 month regimen. Seroprotection rates and hSBA GMTs one month following the fourth dose at 12 months were indicative of a booster response for both regimens.

Table 3: Serum bactericidal antibody responses following a booster at 12 months of age after a primary series administered at 2, 3 and 4 (Study V72P12E1) or 2, 4 and 6 months of age (Study V72P13E1), and persistence of bactericidal antibody one year after the booster (Study V72P13E2).

Antigen*	Response (95% CI)	2, 3, 4, 12 months	2, 4, 6, 12 months
fHBP	pre-booster** % seropositive*** hSBA GMT****	N=81 58% (47-69) 5.79 (4.54-7.39)	N=426 82% (78-85) 10 (9.55-12)
	1 month after booster % seropositive hSBA GMT	N=83 100% (96-100) 135 (108-170)	N=422 100% (99-100) 128 (118-139)
	12 months after booster % seropositive hSBA GMT	-	N=299 62% (56-67) 6.5 (5.63-7.5)
NadA	pre-booster % seropositive hSBA GMT	N=79 97% (91-100) 63 (49-83)	N=423 99% (97-100) 81 (74-89)
	1 month after booster % seropositive hSBA GMT	N=84 100% (96-100) 1558 (1262-1923)	N=421 100% (99-100) 1465 (1350-1590)
	12 months after booster % seropositive hSBA GMT	-	N=298 97% (95-99) 81 (71-94)
PorA P1.4	pre-booster % seropositive hSBA GMT	N=83 19% (11-29) 1.61 (1.32-1.96)	N=426 22% (18-26) 2.14 (1.94-2.36)
	1 month after booster % seropositive hSBA GMT	N=86 97% (90-99) 47 (36-62)	N=424 95% (93-97) 35 (31-39)
	12 months after booster % seropositive hSBA GMT	-	N=300 17% (13-22) 1.91 (1.7-2.15)

NHBA	pre-booster % seropositive hSBA GMT	N=69 25% (15-36) 2.36 (1.75-3.18)	N=100 61% (51-71) 8.4 (6.4-11)
	1 month after booster % seropositive hSBA GMT	N=67 76% (64-86) 12 (8.52-17)	N=100 98% (93-100) 42 (36-50)
	12 months after booster % seropositive hSBA GMT	-	N=291 36% (31-42) 3.35 (2.88-3.9)

* The following strains of group B meningococci, which were isolated from cases of invasive disease, were used to assess functional immunogenicity against each of the vaccine antigens by hSBA:

- fHBP antigen: strain 44/76
- NadA antigen: strain 5/99
- immunodominant PorA P1.4 component of OMV: strain NZ98/254
- NHBA antigen: strain M10713

** pre-booster time point represents persistence of bactericidal antibody at 8 months after BEXSERO vaccination at 2, 3 and 4 months of age and 6 months after BEXSERO vaccination at 2, 4 and 6 months of age.

*** % seropositive = the percentage of participants who achieved an hSBA \geq 1:5.

**** GMT = geometric mean titre.

A decline in antibody titers to PorA P1.4 and fHbp antigens (reaching 9%-10% and 12%-20% of subjects with an hSBA \geq 1:5, respectively) has been observed in an additional study in children 4 years of age who received a full priming and booster schedule as infants. In the same study the response to a further dose was indicative of immunological memory as 81%-95% of subjects reached an hSBA \geq 1:5 to PorA P1.4 and 97%-100% to fHbp antigens following further vaccination. The clinical significance of this observation and the need for additional booster doses to maintain longer term protective immunity has not been established.

Two-dose primary schedule followed by a booster

The immunogenicity after two doses (at 3 and a half and 5 months of age) or three doses (at 2 and a half, 3 and a half and 5 months of age) of BEXSERO followed by a booster, has been evaluated in an additional phase 3 clinical study (V72_28). The percentages of seropositive subjects (i.e. achieving an hSBA of at least 1:4 to the fHPB, NadA, PorA P1.4 and/or NHBA antigens) ranged from 44% to 100% one month after the second dose and from 55% to 100% one month after the third dose. At one month following a booster administered 6 months after the last dose, the percentages of seropositive to the fHPB, NadA, PorA P1.4 and/or NHBA antigens ranged from 87% to 100% for the two-dose schedule, and from 83% to 100% for the three-dose schedule.

Antibody persistence was evaluated in an extension study in children 3 to 4 years of age (V72_28E1). Comparable percentages of subjects were seropositive at 2 to 3 years after being previously vaccinated in infancy with either two doses followed by a booster of BEXSERO at 11 months (ranging from 35% to 91%) or three doses in infancy followed by a booster at 11 months (ranging from 36% to 84%). In the same study the response to an additional dose administered 2 to 3 years after the 11-month booster was indicative of immunological memory as shown by a robust antibody response against all 4 BEXSERO antigens, ranging from 81% to 100% and from 70% to 99%, respectively. These observations are consistent with adequate

priming in infancy with both a two-dose and a three-dose primary series followed by a booster of BEXSERO.

Immunogenicity in infants 6 months to 11 months of age and children 12 to 23 months of age

Bactericidal responses following two doses administered two months apart to children 6 months to 23 months of age were investigated in two studies (V72P9 and V72P13E1). Baseline GMTs were uniformly low against all reference strains in each study, ranging from 1.00 to 2.32. After the two-dose series seropositivity rates and hSBA GMTs were high against each of the vaccine antigens and were similar for infants vaccinated at 6 and 8 months of age and toddlers vaccinated at 13 and 15 months of age. (See Table 4). Data on antibody persistence one year after the two doses at 13 and 15 months of age are also summarised in Table 4 (V72P13E2).

Table 4: Serum bactericidal antibody responses following BEXSERO vaccination at 6 and 8 months of age (Study V72P9), or 13 and 15 months of age (Study V72P13E1) and persistence of bactericidal antibody one year after the two doses at 13 and 15 months of age (Study V72P13E2).

Antigen*	Response (95% CI)	Age of vaccination	
		6, 8 months	13, 15 months
fHBP	<u>1 month after 2nd dose</u> % seropositive** hSBA GMT***	N=23 100% (85-100) 250 (173-361)	N=163 100% (98-100) 271 (237-310)
	<u>12 months after 2nd dose</u> % seropositive hSBA GMT	-	N=68 74% (61-83) 14 (9.4-20)
NadA	<u>1 month after 2nd dose</u> % seropositive hSBA GMT	N=23 100% (85-100) 534 (395-721)	N=164 100% (98-100) 599 (520-690)
	<u>12 months after 2nd dose</u> % seropositive hSBA GMT	-	N=68 97% (90-100) 70 (47-104)
PorA P1.4	<u>1 month after 2nd dose</u> % seropositive hSBA GMT	N=22 95% (77-100) 27 (21-36)	N=164 100% (98-100) 43 (38-49)
	<u>12 months after 2nd dose</u> % seropositive hSBA GMT	-	N=68 18% (9-29) 1.65 (1.2-2.28)
NHBA	<u>1 month after 2nd dose</u> % seropositive hSBA GMT	-	N=46 63% (48-77) 11 (7.07-16)
	<u>12 months after 2nd dose</u> % seropositive hSBA GMT	-	N=65 38% (27-51) 3.7 (2.15-6.35)

* The following strains of group B meningococci, which were isolated from cases of invasive disease, were used to assess functional immunogenicity against each of the vaccine antigens by hSBA:

- fHBP antigen: strain 44/76
- NadA antigen: strain 5/99
- immunodominant PorA P1.4 component of OMV: strain NZ98/254
- NHBA antigen: strain M10713

** % seropositive = the percentage of participants who achieved an hSBA \geq 1:4 (in the 6 to 11 months of age) in study V72P9 and an hSBA \geq 1:5 (in the 12 to 23 month age range) in studies V72P13E1 and V72P13E2.

***GMT = geometric mean titre.

An increase in hSBA titres for the four reference strains was recorded in an additional group of 43-68 children evaluated after vaccination with BEXSERO at 12 and 14 months of age in study V72P13E1. Post-vaccination seropositivity rates were: 100% for strain 44/76 and strain 5/99; 96% for strain NZ98/254; and 74% for strain M10713.

Immunogenicity in children 2 to 10 years of age

The immunogenicity after two doses of BEXSERO administered either one or two months apart in children 2 to 10 years of age has been evaluated in two phase 3 clinical studies (V72_28 and V72_28E1). In the first study (V72_28), whose results are summarised in Table 5, participants received two doses of BEXSERO two months apart. The seroresponse rates and hSBA GMTs were high after the two-dose schedule in children against each of the vaccine antigens (Table 5).

Table 5. Serum bactericidal antibody responses at 1 month following the second dose of BEXSERO given to children 2-10 years of age following a 0, 2-month schedule

Antigen		2 to 5 years of age	6 to 10 years of age
fHbp	% seropositive* (95% CI)	N=99 100% (96-100)	N=287 99% (96-100)
	hSBA GMT** (95% CI)	140 (112-175)	112 (96-130)
NadA	% seropositive (95% CI)	N=99 99% (95-100)	N=291 100% (98-100)
	hSBA GMT (95% CI)	584 (466-733)	457 (392-531)
PorA P1.4	% seropositive (95% CI)	N=100 98% (93-100)	N=289 99% (98-100)
	hSBA GMT (95% CI)	42 (33-55)	40 (34-48)
NHBA	% seropositive (95% CI)	N=95 91% (83-96)	N=275 95% (92-97)
	hSBA GMT (95% CI)	23 (18-30)	35 (29-41)

* % seropositive = the percentage of subjects who achieved an hSBA \geq 1:4 (against reference strains for fHbp, NadA, PorA P1.4 antigens) and an hSBA \geq 1:5 (against reference strain for NHBA antigen).

** GMT = geometric mean titre.

High percentages of subjects aged 3-10 years were seropositive in the second study (V72_28E1), in which two doses of BEXSERO were administered one month apart. An early immune response after the first dose was also evaluated. The percentages of seropositive subjects (i.e. achieving an hSBA of at least 1:4) against fHPB, NadA, PorA P1.4 and/or NHBA antigens ranged from 46% to 95% at one month after the first dose and from 69% to 100% at one month after the second dose.

Immunogenicity in adolescents (from 11 years of age) and adults

Participants aged 11 to 17 years (study V72P10) received two doses of BEXSERO with a 1, 2 or 6 month interval between doses. Baseline GMTs ranged from 2.64 to 4.11. As early as one month after the first dose, percentages of participants who achieved an hSBA \geq 1:4 ranged from 90% to 97%. Antibody persistence was demonstrated 18 – 23 months after the second dose (see Table6). Independent of pre-vaccination seropositivity status, a high percentage of participants were seropositive and achieved 4-fold increases in hSBA titres post vaccination (see Table 7).

Table6: Serum bactericidal antibody responses in adolescents one month after one and two doses of BEXSERO administered according to different two-dose schedules and persistence of bactericidal antibody 18 to 23 months after the second dose.

Antigen*	Response (95% CI)	0, 1 months	0, 2 months	0, 6 months
fHPB	1 month after 1 st dose	N=677	N=342	N=112
	% seropositive**	94% (92-96)	92% (88-94)	92% (85-96)
	hSBA GMT***	60 (53-69)	52 (43-63)	46 (33-63)
	1 month after 2 nd dose	N=638	N=319	N=86
	% seropositive	100% (99-100)	100% (99-100)	100% (99-100)
	hSBA GMT	210 (193-229)	234 (209-263)	218 (157-302)
	18-23 months after 2 nd dose	N=102	N=106	N=49
	% seropositive	82% (74-89)	81% (72-88)	84% (70-93)
	hSBA GMT	29 (20-42)	34 (24-49)	27 (16-45)
NadA	1 month after 1 st dose	N=677	N=342	N=111
	% seropositive	97% (95-98)	96% (94-98)	97% (92-99)
	hSBA GMT	73 (64-82)	69 (58-82)	81 (61-109)
	1 month after 2 nd dose	N=639	N=320	N=86

Antigen*	Response (95% CI)	0, 1 months	0, 2 months	0, 6 months
	% seropositive	100% (99-100)	99% (98-100)	99% (94-100)
	hSBA GMT	490 (455-528)	734 (653-825)	880 (675-1147)
	18-23 months after 2 nd dose	N=102	N=106	N=49
	% seropositive	93% (86-97)	95% (89-98)	94% (83-99)
	hSBA GMT	40 (30-54)	43 (33-58)	65 (43-98)
PorA P1.4	1 month after 1 st dose	N=677	N=342	N=111
	% seropositive	94% (92-96)	92% (88-94)	90% (83-95)
	hSBA GMT	49 (43-55)	40 (33-47)	42 (31-56)
	1 month after 2 nd dose	N=639	N=319	N=86
	% seropositive	100% (99-100)	100% (99-100)	100% (96-100)
	hSBA GMT	92 (84-102)	123 (107-142)	140 (101-195)
	18-23 months after 2 nd dose	N=102	N=106	N=49
	% seropositive	75% (65-83)	75% (66-83)	86% (73-94)
hSBA GMT	17 (12-24)	19 (14-27)	27 (17-43)	
NHBA	1 month after 2 nd dose	N=46	N=46	-
	% seropositive	100% (92-100)	100% (92-100)	-
	hSBA GMT	99 (76-129)	107 (82-140)	-

* The following strains of group B meningococci, which were isolated from cases of invasive disease, were used to assess functional immunogenicity against each of the vaccine antigens by hSBA:

- fHBP antigen: strain 44/76
- NadA antigen: strain 5/99
- immunodominant PorA P1.4 component of OMV: strain NZ98/254

** % seropositive = the percentage of participants who achieved an hSBA \geq 1:4

***GMT = geometric mean titre.

Table 7: Percentage of adolescents with seroresponse and at least 4-fold rise in bactericidal titres one month after one and two doses of BEXSERO administered according to different two-dose schedules - stratified by pre-vaccination titres.

Antigen*	Response (95% CI)		0, 1 months	0, 2 months	0, 6 months	
fhBP	% seropositive** after 1 st dose	pre-vaccination titre <1:4	N=388 90% (87-93)	N=193 86% (80-91)	N=65 86% (75-93)	
		pre-vaccination titre ≥1:4	N=289 100% (98-100)	N=149 99% (95-100)	N=47 100% (92-100)	
	% 4-fold increase after 1 st dose	pre-vaccination titre <1:4	N=388 87% (84-91)	N=193 84% (78-89)	N=65 86% (75-93)	
		pre-vaccination titre ≥1:4	N=289 71% (65-76)	N=149 68% (60-75)	N=47 62% (46-75)	
	% seropositive after 2 nd dose	pre-vaccination titre <1:4	N=369 100% (98-100)	N=179 100% (98-100)	N=55 100% (94-100)	
		pre-vaccination titre ≥1:4	N=269 100% (99-100)	N=140 100% (97-100)	N=31 100% (89-100)	
	% 4-fold increase after 2 nd dose	pre-vaccination titre <1:4	N=369 100% (98-100)	N=179 100% (98-100)	N=55 100% (94-100)	
		pre-vaccination titre ≥1:4	N=268 90% (86-93)	N=140 86% (80-92)	N=31 90% (74-98)	
	NadA	% seropositive after 1 st dose	pre-vaccination titre <1:4	N=454 95% (93-97)	N=223 96% (92-98)	N=79 96% (89-99)
			pre-vaccination titre ≥1:4	N=223 100% (98-100)	N=119 98% (94-100)	N=32 100% (89-100)
		% 4-fold increase after 1 st dose	pre-vaccination titre <1:4	N=454 94% (92-96)	N=223 95% (91-98)	N=79 96% (89-99)
			pre-vaccination titre ≥1:4	N=223 74% (67-79)	N=119 72% (63-80)	N=32 69% (50-84)
% seropositive after 2 nd dose		pre-vaccination titre <1:4	N=427 100% (99-100)	N=211 99% (97-100)	N=64 98% (92-100)	
		pre-vaccination titre ≥1:4	N=212 100% (98-100)	N=109 100% (97-100)	N=22 100% (85-100)	
% 4-fold increase after 2 nd dose		pre-vaccination titre <1:4	N=426 99% (98-100)	N=211 99% (97-100)	N=64 98% (92-100)	
		pre-vaccination titre ≥1:4	N=212 96% (93-98)	N=109 95% (90-98)	N=22 95% (77-100)	
PorA P1.4	% seropositive after 1 st dose	pre-vaccination titre <1:4	N=450 91% (88-94)	N=219 87% (82-91)	N=75 85% (75-92)	
		pre-vaccination titre ≥1:4	N=226 100% (98-100)	N=123 100% (97-100)	N=36 100% (90-100)	

Antigen*	Response (95% CI)		0, 1 months	0, 2 months	0, 6 months
	% 4-fold increase after 1 st dose	pre-vaccination titre <1:4	N=450 91% (88-94)	N=219 85% (80-90)	N=75 85% (75-92)
		pre-vaccination titre ≥1:4	N=226 64% (57-70)	N=123 55% (46-64)	N=36 64% (46-79)
	% seropositive after 2 nd dose	pre-vaccination titre <1:4	N=427 100% (98-100)	N=208 100% (98-100)	N=64 100% (94-100)
		pre-vaccination titre ≥1:4	N=212 100% (98-100)	N=111 100% (97-100)	N=22 100% (85-100)
	% 4-fold increase after 2 nd dose	pre-vaccination titre <1:4	N=426 99% (98-100)	N=208 100% (98-100)	N=64 100% (94-100)
		pre-vaccination titre ≥1:4	N=211 81% (75-86)	N=111 77% (68-84)	N=22 82% (60-95)
NHBA	% seropositive after 2 nd dose	pre-vaccination titre <1:4	N=2 100% (16-100)	N=9 100% (66-100)	-
		pre-vaccination titre ≥1:4	N=44 100% (92-100)	N=37 100% (91-100)	-
	% 4-fold increase after 2 nd dose	pre-vaccination titre <1:4	N=2 100% (16-100)	N=9 89% (52-100)	-
		pre-vaccination titre ≥1:4	N=44 30% (17-45)	N=37 19% (8-35)	-

* The following strains of group B meningococci, which were isolated from cases of invasive disease, were used to assess functional immunogenicity against each of the vaccine antigens by hSBA:

- fHBP antigen: strain 44/76
- NadA antigen: strain 5/99
- immunodominant PorA P1.4 component of OMV: strain NZ98/254

** % seropositive = the percentage of participants who achieved an hSBA ≥ 1:4

In studies of adults aged 18 to 50 years (V72P4) and 18 to 40 years (V72P5), data were obtained after the two doses of BEXSERO with a 1 month or 2 month interval between doses. (see Table 8). Baseline GMTs against reference strains ranged from 1.71 to 4.06. Responses in adults were similar to those of adolescents.

Table 8: Serum bactericidal antibody responses in adults after two doses of BEXSERO administered according to different two-dose schedules.

Antigen*	Response (95% CI)	0, 1 months	0, 2 months
fHBP	1 month after 2 nd dose	N=28	N=46
	% seropositive**	100% (88-100)	100% (92-100)
	hSBA GMT***	100 (75-133)	93 (71-121)
NadA	1 month after 2 nd dose	N=28	N=46
	% seropositive	100% (88-100)	100% (92-100)
	hSBA GMT	566 (338-948)	144 (108-193)
PorA P1.4	1 month after 2 nd dose	N=28	N=46
	% seropositive	96% (82-100)	91% (79-98)
	hSBA GMT	47 (30-75)	32 (21-48)

*The following strains of group B meningococci, which were isolated from cases of invasive disease, were used to assess functional immunogenicity against each of the vaccine antigens by hSBA:

- fHBP antigen: strain 44/76
- NadA antigen: strain 5/99
- immunodominant PorA P1.4 component of OMV: strain NZ98/254

** % seropositive = the percentage of participants who achieved an hSBA \geq 1:4.

*** GMT = geometric mean titre.

Serum bactericidal response to NHBA antigen has not been evaluated.

Immunogenicity in special populations

Children and adolescents with complement deficiencies, asplenia, or splenic dysfunction

In a phase 3 clinical study, children and adolescents 2 to 17 years of age with complement deficiencies (40), with asplenia or splenic dysfunction (107), and age-matched healthy participants (85) received two doses of BEXSERO two months apart. At 1 month following the 2-dose vaccination course, the percentages of participants with hSBA $\geq 1:5$ in individuals with complement deficiencies and asplenia or splenic dysfunction were 87% and 97% for antigen fHbp, 95% and 100% for antigen NadA, 68% and 86% for antigen PorA P1.4, 73% and 94% for antigen NHBA, respectively, indicating an immune response in these immunocompromised participants. The percentages of healthy participants with hSBA $\geq 1:5$ were 98% for antigen fHbp, 99% for antigen NadA, 83% for antigen PorA P1.4, and 99% for antigen NHBA.

Impact of vaccination on disease incidence

In the UK, BEXSERO was introduced into the national immunisation programme (NIP) in September 2015 using a two-dose schedule in infants (at 2 and 4 months of age) followed by a booster dose (at 12 months of age). In this context, Public Health England conducted a 3-year observational study at the national level covering the entire birth cohort.

After three years of the programme, a statistically significant reduction of 75% [Incidence Rate Ratio 0.25 (95% CI: 0.19;0.36)] in cases of IMD caused by Neisseria meningitidis group B was observed in vaccine-eligible infants, irrespective of the infants' vaccination status or predicted meningococcal group B strain coverage.

5.2 Pharmacokinetic properties

Not applicable for vaccines.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on repeat-dose toxicity and reproductive and developmental toxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Histidine

Sucrose

Water for Injections

For adsorbent see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Protect from light.

6.5 Nature and contents of container

0.5 mL suspension in a pre-filled syringe (Type I glass) with a plunger stopper (Type I bromobutyl rubber) and with a protective tip cap (Type II rubber).

Pack sizes of 1 syringe with or without needle or 10 syringes without needles.

Not all pack sizes may be distributed in New Zealand.

6.6 Special precautions for disposal and other handling

Upon storage of the suspension, a fine off-white deposit may form. Shake the vaccine well before use to form a homogeneous suspension. The vaccine should be visually inspected for particulate matter and discoloration prior to administration. In the event of any foreign particulate matter and/or variation of physical aspect being observed, do not administer the vaccine.

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown
Auckland
New Zealand

Phone: (09) 367 2900

Facsimile: (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
19 July 2018.

10. DATE OF REVISION OF THE TEXT

31 March 2020

Summary table of changes

Section changed	Summary of new information
4.8	Addition of rash (in adolescents from 11 years of age and adults) as a new adverse reaction in the post-marketing section
5.1	Update of data from UK study V72_38OB

Version 4.0

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