

## **NAME OF THE MEDICINE**

BEXSERO<sup>®</sup> suspension for injection  
Multicomponent Meningococcal group B Vaccine (recombinant, adsorbed)  
Pharmacotherapeutic group: Meningococcal vaccines, ATC code: J07AH09.

## **DESCRIPTION**

BEXSERO is a multicomponent Meningococcal group B vaccine presented as a suspension for injection in a pre-filled syringe containing purified recombinant meningococcal protein antigens expressed in *E. coli* and outer membrane vesicles (OMV) derived from *N. meningitidis* group B. Bactericidal antibodies directed against components of the bacterium protect against Invasive Meningococcal Disease (IMD).

1 dose (0.5 mL) of BEXSERO contains:

<i>Neisseria meningitidis</i> Group B Neisseria Heparin Binding Antigen fusion protein <sup>1,2</sup> (rbe)	- 50 micrograms
<i>Neisseria meningitidis</i> Group B Neisseria Adhesin A protein <sup>1,2</sup> (rbe)	- 50 micrograms
<i>Neisseria meningitidis</i> Group B Factor H Binding Protein fusion protein <sup>1,2</sup> (rbe)	- 50 micrograms
Outer membrane vesicles (OMV) from <i>Neisseria meningitidis</i> group B strain NZ98/254 measured as amount of total protein containing the PorA P1.4 <sup>2</sup>	- 25 micrograms

<sup>1</sup>Produced 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.

<sup>2</sup>Adsorbed on aluminium hydroxide (0.5 mg Al<sup>3+</sup>).

BEXSERO contains the excipients sodium chloride, histidine, sucrose, and water for injections.

## **Appearance**

White opalescent liquid suspension.

BEXSERO is supplied in a 1.0 mL (Type I glass) pre-filled syringe. Syringes are sealed with a plunger stopper (Type I bromobutyl rubber) and with a protective tip cap (Type I or Type II rubber).

## **PHARMACOLOGY**

### **Mechanism of Action**

Immunisation with BEXSERO is intended to stimulate the production of bactericidal antibodies that recognize the vaccine antigens NHBA, NadA, fHBP, and PorA P1.4 (the immunodominant antigen present in the OMV component) and is protective against Invasive Meningococcal Disease (IMD). Meningococci that express these antigens at sufficient levels are susceptible to killing by vaccine-elicited antibodies.

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

### **Epidemiological Data**

Invasive meningococcal disease (IMD) is an important cause of meningitis and septicemia, which can lead to mortality (8.1% in Europe), or permanent sequelae (11-19%). According to the National Notifiable Diseases Surveillance System, the majority of IMD in Australia is caused by group B (88% in 2009). The highest incidence of group B disease occurs in children under 4 years of age (5 notifications per 100,000 population), followed by a peak in children from 15 to 19 years of age (2 notifications per 100,000 population).

Group B has caused prolonged outbreaks due to hypervirulent strains in New Zealand, with high incidences in infants (less than 1 year: 124 cases per 100,000), and children (1 to 4 years: 60 cases per 100,000).

Protection from meningococcal disease correlates with the presence of serum antibodies able to kill the bacteria in the presence of human complement. The potential of BEXSERO to induce antibodies able to kill diverse strains of invasive meningococcal group B bacteria was studied using a novel typing method, the Meningococcal Antigen Typing System (MATS). MATS was developed to relate vaccine antigen content and expression among different strains of meningococcal group B bacteria to killing of the strains in the serum bactericidal assay with human complement (hSBA) by pooled serum from 13 month old infants immunized at 2, 4 and 6 months of age with a booster at 12

months of age. 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% Confidence Interval: 63%-87%) of meningococcal group B isolates were predicted to be killed in hSBA based on their MATS vaccine antigen type.

## **CLINICAL TRIALS**

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, 44/76, 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 44/76 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 subjects 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. A threshold of 1:5 was then set after further hSBA assay validation to ensure, based on the intermediate precision of the assay, 95% certainty of a true response of 1:4, this cutoff was used to define seropositive responses in late-stage clinical studies in infants (V72P13, V72P12 and V72P13E1).

Immunogenicity was evaluated in randomised, multicentre, clinical trials that enrolled infants, adolescents and adults.

#### ***Immunogenicity in infants***

In infant study V72P13, participants received three doses of BEXSERO at 2, 4 and 6 months of age with concomitant routine vaccines. In infant study V72P12, participants received three doses of BEXSERO at either 2, 4 and 6 or 2, 3, and 4 months of age. Sera were obtained both before vaccination and one month after the third vaccination (see Table 1 below). In the extension study of V72P13 (V72P13E1), participants who received three doses of BEXSERO at 2, 4 and 6 months of age received a booster dose at 12

months of age (see Table 2 below), whereas previously unvaccinated toddlers received two doses in the second year of life (see Table 3 below). The immunogenicity after two doses of BEXSERO has been also documented in another study in infants (V72P9) aged 6 months to 8 months at enrolment (see Table 3 below).

Immunogenicity results at one month after three doses of BEXSERO administered at 2, 3, 4 and 2, 4, 6 months of age are summarised in Table 1.

**Table 1. Serum bactericidal antibody responses 1 month following BEXSERO vaccination at 2, 3, 4 (Study V72P12) and 2, 4, 6 (Study V72P13) months of age**

Antigen*		V72P12	V72P13
fHBP		N=273	N=1149
	% seropositive** (95% CI)	99% (97-100)	100% (99-100)
	hSBA GMTs*** (95% CI)	82 (75-91)	91 (87-95)
NadA		N=275	N=1152
	% seropositive (95% CI)	100% (99-100)	100% (99-100)
	hSBA GMTs (95% CI)	325 (292-362)	635 (606-665)
PorA P1.4		N=274	N=1152
	% seropositive (95% CI)	81% (76-86)	84% (82-86)
	hSBA GMTs (95% CI)	11 (9.14-12)	14 (13-15)
NHBA			N=100
	% seropositive (95% CI)	Not Done	84% (75-91)
	hSBA GMTs (95% CI)	Not Done	16 (13-21)

\* 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 subjects who achieved an hSBA  $\geq$  1:5.

\*\*\*GMTs = geometric mean titers.

Baseline geometric mean titers (GMTs) were uniformly low against all four reference strains in the BEXSERO (ranging from 1.05 to 3.15) and the control groups (ranging from 1.01 to 1.28) in both studies. The bactericidal responses one month after the third vaccination against meningococcal reference strains were high against the fHBP, NadA,

PorA P1.4 and NHBA antigens at both schedules in the BEXSERO groups (see Table 1 above). In contrast, the mean hSBA GMTs following routine vaccination alone remained low and similar with respect to the baseline in the control groups (ranging from 1.04 to 1.25).

Data on bactericidal antibody responses to a booster (fourth) dose of BEXSERO at 12 months of age following vaccinations at 2, 4 and 6 months of age (V72P13E1) are summarised in Table 2 below. The immune responses one month after the vaccination were high and indicative of a booster response. The results also show that bactericidal antibodies persisted at 6 months after the three-dose infant primary series, at the pre-booster time point (V72P13E1), and one year after the booster dose (V72P13E2). Data on antibody persistence one year after the booster are summarised in Table 2.

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

Antigen*		hSBA GMTs***	% Seropositive**
<b>fHBP</b>	Pre-Booster (95% CI)	N=426 10 (9.55-12)	N=426 82% (78-85)
	1 Month After Booster (95% CI)	N=422 128 (118-139)	N=422 100% (99-100)
	12 months after Booster (95% CI)	N=299 6.5 (5.63-7.5)	N=299 62% (56-67)
<b>NadA</b>	Pre-Booster (95% CI)	N=423 81 (74-89)	N=423 99% (97-100)
	1 Month After Booster (95% CI)	N=421 1465 (1350-1590)	N=421 100% (99-100)
	12 months after Booster (95% CI)	N=298 81 (71-94)	N=298 97% (95-99)
<b>PorA P1.4</b>	Pre-Booster (95% CI)	N=426 2.14 (1.94-2.36)	N=426 22% (18-26)
	1 Month After Booster (95% CI)	N=424 35 (31-39)	N=424 95% (93-97)
	12 months after Booster (95% CI)	N=300 1.91 (1.7-2.15)	N=300 17% (13-22)
<b>NHBA</b>	Pre-Booster (95% CI)	N=100 8.4 (6.4-11)	N=100 61% (51-71)
	1 Month After Booster (95% CI)	N=100 42 (36-50)	N=100 98% (93-100)
	12 months after Booster (95% CI)	N=291 3.35 (2.88-3.9)	N=291 36% (31-42%)

\* 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 subjects who achieved an hSBA  $\geq$  1:5.

\*\*\*GMTs = geometric mean titers.

*Immunogenicity in infants aged 6 months and older, and toddlers*

Bactericidal responses after two doses in older infants and toddlers have been documented in two studies whose results are summarised in Table 3 below. Against each of the vaccine antigens, seroresponse rates and hSBA GMTs were high and similar after the two-dose series in both infants and toddlers. Baseline GMTs were uniformly low against all reference strains in both studies (ranging from 1.00 to 1.94).

Data on antibody persistence one year after the two doses at 13 and 15 months of age are summarized in Table 3.

The increase in hSBA titers for the four reference strains was similar in an additional group of 43-68 subjects evaluated after vaccination with BEXSERO at 12 and 14 months of age. A similar response was observed in terms of percentages of seropositive subjects (100% for strain 44/76 and strain 5/99; 96% for strain NZ98/254; and 74% for strain M10713).

**Table 3. Serum bactericidal antibody responses following BEXSERO vaccination at 6 to 8 months of age and 2 months after (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*		V72P9	V72P13E1 / V72P13E2
fHBP	1 month after 2 <sup>nd</sup> dose % seropositive** (95% CI) hSBA GMTs*** (95% CI)	N=23 100% (85-100) 250 (173-361)	N=163 100% (98-100) 271 (237-310)
	12 months after 2 <sup>nd</sup> dose % seropositive (95% CI) hSBA GMTs (95% CI)	Not Done	N=68 74% (61-83) 14 (9.4-20)
NadA	1 month after 2 <sup>nd</sup> dose % seropositive (95% CI) hSBA GMTs (95% CI)	N=23 100% (85-100) 534 (395-721)	N=164 100% (98-100) 599 (520-690)
	12 months after 2 <sup>nd</sup> dose % seropositive (95% CI) hSBA GMTs (95% CI)	Not Done	N=68 97% (90-100) 70 (47-104)
PorA P1.4	1 month after 2 <sup>nd</sup> dose % seropositive (95% CI) hSBA GMTs (95% CI)	N=22 95% (77-100) 27 (21-36)	N=164 100% (98-100) 43 (38-49)
	12 months after 2 <sup>nd</sup> dose % seropositive (95% CI) hSBA GMTs (95% CI)	Not Done	N=68 18% (9-29) 1.65 (1.2-2.28)
NHBA	1 month after 2 <sup>nd</sup> dose % seropositive (95% CI) hSBA GMTs (95% CI)	Not Done	N=46 63% (48-77) 11 (7.07-16)
	12 months after 2 <sup>nd</sup> dose % seropositive (95% CI) hSBA GMTs (95% CI)	Not Done	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 subjects who achieved an hSBA  $\geq$  1:4 in study V72P9 and hSBA  $\geq$  1:5 in studies V72P13E1 and V72P13E2.

\*\*\*GMTs = geometric mean titers.



*Immunogenicity in individuals aged 11 years and older*

In adolescents study (V72P10), participants received two doses of BEXSERO with a one, two or six month interval between doses, as shown in Table 4 below.

In other studies in adults (V72P4 and V72P5), data were also obtained after two doses of BEXSERO with a one month or two month interval between doses (see Table 4 below).

The vaccination schedules of two doses administered with an interval of one or two months showed similar immune responses in both adults (V72P4, V72P5) and adolescents (V72P10). Similar responses were also observed for adolescents administered two doses of BEXSERO with an interval of six months (V72P10).

Baseline GMTs were also similar against the reference strains in all studies both in adolescents (ranging from 2.64 to 4.11) and in adults (ranging from 1.71 to 4.06).

**Table 4: Serum bactericidal antibody responses in adults or adolescents administered two different dose schedules of BEXSERO measured one month after the second dose**

Antigen*		V72P5 0, 1 months	V72P10 0, 1 months	V72P4 0, 2 months	V72P10 0, 2 months	V72P10 0, 6 months
<b>fHBP</b>	% seropositive** (95% CI)	N=28 100% (88-100)	N=637 100% (99-100)	N=46 100% (92-100)	N=319 100% (99-100)	N=86 100% (96-100)
	hSBA GMTs*** (95% CI)	100 (75-133)	210 (193-229)	93 (71-121)	212 182-246	218 (157-302)
<b>NadA</b>	% seropositive (95% CI)	N=28 100% (88-100)	N=638 100% (99-100)	N=46 100% (92-100)	N=320 99% (98-100)	N=86 99% (94-100)
	hSBA GMTs (95% CI)	566 (338-948)	490 (455-528)	144 (108-193)	713 626-812	880 (675-1147)
<b>PorA P1.4</b>	% seropositive (95% CI)	N=28 96% (82-100)	N=638 100% (99-100)	N=46 91% (79-98)	N=319 100% (99-100)	N=86 100% (96-100)
	hSBA GMTs (95% CI)	47 (30-75)	92 (84-102)	32 (21-48)	123 (104-145)	140 (101-195)

\* 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 subjects who achieved an hSBA  $\geq$  1:4

\*\*\*GMTs = geometric mean titers.

In study V72P10, bactericidal responses following two doses of BEXSERO were stratified by baseline hSBA less than 1:4 or equal to or greater than 1:4. The percentage of subjects with at least a 4-fold increase in hSBA titer from baseline to one month after the second dose of BEXSERO is summarised in Table 5 below. A high percentage of subjects achieved 4-fold increase responses to vaccination independent of pre-vaccination titer.

**Table 5: Percentage of subjects with at least 4-fold rise in bactericidal titers from pre- to post-vaccination, stratified by pre-vaccination titers measured one month after the second dose**

Antigen*		V72P10 0, 1 months	V72P10 0, 2 months	V72P10 0, 6 months
<b>fHBP</b>	Pre-vaccination titer <1:4 (95% CI)	N=369 100% (98-100)	N=179 100% (98-100)	N=55 100% (94-100)
	Pre-vaccination titer ≥1:4 (95% CI)	N=268 90% (86-93)	N=140 86% (80-92)	N=31 90% (74-98)
<b>NadA</b>	Pre-vaccination titer <1:4 (95% CI)	N=426 99% (98-100)	N=211 99% (97-100)	N=64 98% (92-100)
	Pre-vaccination titer ≥1:4 (95% CI)	N=212 96% (93-98)	N=109 95% (90-98)	N=22 95% (77-100%)
<b>PorA P1.4</b>	Pre-vaccination titer <1:4 (95% CI)	N=426 99% (98-100)	N=208 100% (98-100)	N=64 100% (94-100)
	Pre-vaccination titer ≥1:4 (95% CI)	N=211 81% (75-86)	N=111 77% (68-84)	N=22 82% (60-95)

\* 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

## **INDICATIONS**

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.

## **CONTRAINDICATIONS**

Hypersensitivity to the active substances or to any of the excipients listed in section DESCRIPTION.

## **PRECAUTIONS**

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.

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.

BEXSERO is not expected to provide protection against all circulating meningococcal group B strains (see PHARMACOLOGY).

As with many vaccines, the health care professional 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 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. In the same study, fever  $\geq 39.5^{\circ}\text{C}$  was reported by 5%, 7% and 4% of subjects after dose 1, 2 and 3, respectively, in the BEXSERO vaccine group, compared with 1%, 1% and 2% 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.

There are no data on the use of BEXSERO in subjects with impaired immune responsiveness. In immunocompromised individuals, vaccination may not result in a protective antibody response.

There are no data on the use of BEXSERO in subjects above 50 years of age or in patients with chronic medical conditions.

The tip cap of the syringe may contain natural rubber latex. Although the risk for developing allergic reactions is very small, health care professionals should consider the benefit-risk prior to administering this vaccine to subjects with known history of hypersensitivity to latex.

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.

No studies on the effects on the ability to drive and use machines have been performed. However, some of the effects mentioned under section ADVERSE EFFECTS may temporarily affect the ability to drive or use machines.

### **Effects on 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.

### **Use in Pregnancy (Category B1)**

Insufficient clinical data on exposed pregnancies are available.

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

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.

### **Use in Lactation**

Information on the safety of the vaccine during lactation is not available. The benefit-risk ratio must be examined before making the decision to immunise during lactation.

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

### **Genotoxicity**

Genotoxicity studies have not been performed with BEXSERO.

### **Carcinogenicity**

Carcinogenicity studies have not been performed with BEXSERO.

## **INTERACTIONS WITH OTHER MEDICINES**

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 (7-valent) pneumococcal conjugate, measles, mumps, rubella, and varicella.

Clinical studies demonstrated that the immune responses and the safety profiles of the co-administered 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 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.

When given concomitantly with other vaccines BEXSERO should be administered at separate injection sites (see DOSAGE AND ADMINISTRATION).

## **ADVERSE EFFECTS**

Adverse reactions from clinical studies with the BEXSERO are described below.

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 one dose of BEXSERO. Among BEXSERO recipients, 4843 were infants and toddlers, and 1712 were adolescents and adults. Of the subjects who received primary infant series of BEXSERO, 1630 received a booster dose in the second year of life.

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 vaccine, 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.

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 and Toddlers*

Metabolism and nutrition disorders

Very common: eating disorders

Nervous system disorders

Very common: sleepiness, unusual crying,  
Uncommon: seizures (including febrile seizures)

Vascular disorders

Uncommon: pallor (rare after booster)  
Rare: Kawasaki syndrome

Gastrointestinal disorders

Very common: diarrhea, vomiting (uncommon after booster)

Skin and subcutaneous tissue disorders

Very common: rash (uncommon after booster)  
Uncommon: eczema, 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 ( $\geq 40^{\circ}\text{C}$ )

*Adolescents 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

Muscular, connective tissue and bone disorders

Very Common: myalgia, arthralgia

## **DOSAGE AND ADMINISTRATION**

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

### *Infants aged 2 months to 5 months*

The primary infant vaccination schedule consists of three doses, each of 0.5 mL, with an interval of at least 1 month between doses. The first dose should be given at 2 months of age. A booster dose is recommended between 12 months and 23 months of age (see PHARMACOLOGY).

### *Unvaccinated infants aged 6 months to 11 months*

The vaccination schedule consists of 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 with an interval of at least 2 months between the primary series and booster dose. (see PHARMACOLOGY).

### *Unvaccinated toddlers and children aged 12 months to 10 years of age*

The vaccination schedule consists of two doses of 0.5 mL with an interval of at least 2 months between doses. The need for a booster dose after this vaccination schedule has not been established (see PHARMACOLOGY).

### *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 (see PHARMACOLOGY).

### *Individuals above 50 years of age*

There are no data in individuals above 50 years of age.

**Table 6: Summary of Dosages**

<b>Age Group</b>	<b>Primary Immunisation</b>	<b>Intervals between Primary Doses</b>	<b>Booster</b>
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



### **Method of administration**

The vaccine should be 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. 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.

### **OVERDOSAGE**

No case of overdose has been reported.

In case of overdose, immediately contact the Poisons Information Centre on 13 11 26 for advice on management.

### **PRESENTATION AND STORAGE CONDITIONS**

BEXSERO is presented as a 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 I or Type II rubber).

BEXSERO is supplied in packs of 1 syringe with or without needle or packs of 10 syringes without needles. Not all pack sizes may be marketed.

#### **Shelf life and Storage Conditions**

2 years.

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

Upon storage of the suspension product, 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, discard the vaccine.

**Attachment 1: Product information for AusPAR Bexsero; Multi-Component Meningococcal B Vaccine; Novartis Vaccines and Diagnostics Pty Ltd; PM-2011-02486-3-2. Date of finalisation 31 October 2013. This Product Information was approved at the time this AusPAR was published.**

Page 18 of 18

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

## **NAME AND ADDRESS OF THE SPONSOR**

Novartis Vaccines & Diagnostics Pty. Ltd.  
ACN – 089 509 544  
54 Waterloo Road  
North Ryde, NSW 2113

## **POISON SCHEDULE OF THE MEDICINE**

Schedule 4 (Prescription-Only Medicine)

## **DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)**

14 August 2013

---

<sup>®</sup> Registered Trademark of Novartis Vaccines and Diagnostics S.r.l., Italy.

Product Information (PI) and Consumer Medicine Information (CMI) documents are regularly updated.

Please also refer to the TGA web site (<https://www.ebs.tga.gov.au/>) for the most up to date PI and CMI.

**For medical enquiries please contact 1800 671 203 (phone) or [medinfo.phauno@novartis.com](mailto:medinfo.phauno@novartis.com) (email).**

---

Version 1.3

---