NAME OF THE MEDICINE

BEXSERO® 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:

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 P1.4[2]	- 25 micrograms

[1]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.

[2]Adsorbed on aluminium hydroxide (0.5 mg Al^{3+}).

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 II rubber).

PHARMACOLOGY

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.

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 antigen profiles of 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 520 invasive meningococcal group B isolates collected between January 2007 and December 2011 from six Australian states and two Territories showed that 75% (95% Confidence Interval: 61%-86%) 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 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 and V72P10E1). Immunogenicity was evaluated in randomised, multicentre, clinical trials that enrolled infants, children, adolescents and adults.

Three dose primary schedule - infants

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 and one month after booster vaccination. Results are summarised in Table 1.

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 fHPB, 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 2,3,4-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 1. 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 ≥ 1:5.
*** GMT = geometric mean titre.

Table 2 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 2 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 2. 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.

Two dose primary schedule – 6 months to 10 years

Bactericidal responses following two doses administered two months apart to children 6 months to 26 months of age were investigated in three studies (V72P9, V72P13E1 and V72P13E2). Baseline GMTs were uniformly low against all refererence 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, toddlers vaccinated at 13 and 15 months of age, and children vaccinated at 24 and 26 months of age. (See Table 3). Data on antibody persistence one year after the two doses at 13 and 15 months of age are summarized in Table 3.

Table 3. Serum bactericidal antibody responses following BEXSERO vaccination at 6 and 8 months of age (Study V72P9), 13 and 15 months of age or 24 and 26 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	24, 26 months
fHBP	1 month after 2nd dose % seropositive** hSBA GMT***	N=23 100% (85-100) 250 (173-361)	N=163 100% (98-100) 271 (237-310)	N=105 100% (97-100) 220 (186-261)
	12 months after 2nd dose % seropositive hSBA GMT	-	N=68 74% (61-83) 14 (9.4-20)	-
NadA	1 month after 2nd dose % seropositive hSBA GMT	N=23 100% (85-100) 534 (395-721)	N=164 100% (98-100) 599 (520-690)	N=103 99% (95-100) 455 (372-556)
	12 months after 2nd dose % seropositive hSBA GMT	-	N=68 97% (90-100) 70 (47-104)	-
PorA P1.4	1 month after 2nd dose % seropositive hSBA GMT	N=22 95% (77-100) 27 (21-36)	N=164 100% (98-100) 43 (38-49)	N=108 98% (93-100) 27 (23-32)
	12 months after 2nd dose % seropositive hSBA GMT	-	N=68 18% (9-29) 1.65 (1.2-2.28)	-
NHBA	1 month after 2nd dose % seropositive hSBA GMT	-	N=46 63% (48-77) 11 (7.07-16)	N=100 97% (91-99) 38 (32-45)
	12 months after 2nd dose % 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 ≥ 1:4 (in the 6 to 11 months of age) in study V72P9 and hSBA ≥ 1:5 (in the 12 to 23 months and 2 to 10 years of age) 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.

In two studies (V72P6E1 and V72P9E1), a total of 67 children were evaluated after vaccination with two doses of BEXSERO at 40 to 44 months. An increase in hSBA titres for the four reference antigens was observed. Percentages of seropositive participants after the second dose were 100% for fHBP and NadA; 94% and 90% for PorA P1.4; 89% and 72% for NHBA.

Two dose primary schedule – from 11 years

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 ≥ 1:4 ranged from 90% to 97%. Antibody persistence was demonstrated 18 – 23 months after the second dose. (see Table 4). 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 5).

Table 4: 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
fHBP	1 month after 1st 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 2nd 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 2nd 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 1st 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 2nd dose	N=639	N=320	N=86
	% 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 2nd 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 1st 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 2nd 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 2nd dose	N=102	N=106	N=49

Antigen*	Response (95% CI)	0, 1 months	0, 2 months	0, 6 months
	% 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 2nd 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 ≥ 1:4

***GMT = geometric mean titre.

Table 5: 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 1st 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 1st 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 2nd 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 2nd 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 1st 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 1st 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 2nd 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 2nd 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 1st 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)
	% 4-fold increase after 1st 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 2nd 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)

Antigen*	Response (95% CI)		0, 1 months	0, 2 months	0, 6 months
	% 4-fold increase after 2nd 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 2nd 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 2nd 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 6). Baseline GMTs against reference strains ranged from 1.71 to 4.06. Responses in adults were similar to those of adolescents.

Table 6. 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 2nd dose	N=28	N=46
	% seropositive**	100% (88-100)	100% (92-100)
	hSBA GMT***	100 (75-133)	93 (71-121)
NadA	1 month after 2nd 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 2nd 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 ≥ 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 ≥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 ≥1:5 were 98% for antigen fHbp, 99% for antigen NadA, 83% for antigen PorA P1.4, and 99% for antigen NHBA.

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.

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 ADVERSE 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 PHARMACOLOGY).

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 ≥38.0°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 ≥39.5°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 CLINICAL TRIALS).

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 ≤ 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.

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 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.

Use in Lactation

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.

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 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 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 must 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 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 primary infant series of BEXSERO, 3285 received a booster dose in the second year of life. Data for a further 207 children exposed to Bexsero in a subsequent study 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.

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: (≥1/10)
Common: (≥1/100 to <1/10)
Uncommon: (≥1/1,000 to <1/100)
Rare: (≥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: diarrhea, 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 (≥38°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 (≥ 39.5°C)
Uncommon: fever (≥40°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

DOSAGE AND ADMINISTRATION

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

Infants 2 months to 5 months of age

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 CLINICAL TRIALS).

Unvaccinated infants 6 months to 11 months of age

The vaccination schedule consists of two doses, each 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 CLINICAL TRIALS).

Unvaccinated toddlers 12 months to 23 months of age

The vaccination schedule consists of two doses, each 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 CLINICAL TRIALS).

Children 2 years to 10 years of age

The vaccination schedule consists of two doses, each 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 CLINICAL TRIALS).

Adolescents (from 11 years of age) and adults

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 CLINICAL TRIALS).

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

Table 7: Summary of Dosages

Age Group	Primary Immunisation	Intervals between Primary Doses	Booster
Infants, 2 months to 5 months	Three doses each 0.5 mL, with first dose given at 2 months of age [a]	Not less than 1 month	Yes, 1 dose between 12 and 23 months[b]
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]
Unvaccinated 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 2 months	Need not established[b]
Adolescents (from, 11 years of age) and adults*	Two x 0.5 mL	Not less than 1 month	Need not established[b]

[a] The first dose should be given at 2 months of age.
[b] see CLINICAL TRIALS
* 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 subjecs 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.

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
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.

OVERDOSAGE

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

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

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd.
Level 4, 436 Johnston Street
Abbotsford Victoria 3067

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

DATE OF MOST RECENT AMENDMENTS

20 July 2017

Bexsero is a registered trademark of the GSK group of companies.

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.

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