SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

BEXSERO suspension for injection in pre-filled syringe.

Meningococcal group B vaccine (rDNA, component, adsorbed).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

One dose (0,5 mL) contains:

Recombinant *Neisseria meningitidis* group B NHBA fusion protein [1, 2, 3]	50 µg
Recombinant *Neisseria meningitidis* group B NadA protein [1, 2, 3]	50 µg
Recombinant *Neisseria meningitidis* group B fHbp fusion protein [1, 2, 3]	50 µg
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 µg

[1] produced in *E. coli* cells by recombinant DNA technology

[2] adsorbed on aluminium hydroxide (0,5 mg Al^{3+})

[3] NHBA, NadA (*Neisseria* adhesin A), fHbp (factor H binding protein)

Residues:

Kanamycin (used in early manufacturing processes and removed during the later stages of manufacture). If present, kanamycin levels in the final vaccine are less than 0,01 µg per dose).

Contains sugar (sucrose 10 mg/0,5 mL dose).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

Suspension for injection.

White opalescent liquid suspension.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

BEXSERO is indicated for active immunisation of individuals from 2 months of age and older against invasive meningococcal disease caused by *Neisseria meningitidis* group B.

The impact of invasive disease in different age groups as well as the variability of antigen epidemiology for group B strains in different geographical areas should be considered when vaccinating.

See section 5.1 for information on protection against specific group B strains. The use of BEXSERO should be in accordance with official recommendations.

4.2 Posology and method of administration:

Posology:

Table 1. Summary of posology:

Age at first dose	**Primary immunisation**	**Intervals between primary doses**	**Booster**
Infants, 2 months to 5 months [a]	Three doses each of 0,5 mL	Not less than 1 month	Yes, one dose between 12 and 15 months of age with an interval of at least 6 months between the primary series and booster dose [b, c]
	Two doses each of 0,5 mL	Not less than 2 months	
Infants, 6 months to 11 months	Two doses each of 0,5 mL	Not less than 2 months	Yes, one dose in the second year of life with an interval of at least 2 months between the primary series and booster dose [c]
Children, 12 months to 23 months	Two doses each of 0,5 mL	Not less than 2 months	Yes, one dose with an interval of 12 months to 23 months between the primary series and booster dose [c]
Children, 2 years to 10 years	Two doses each of 0,5 mL	Not less than 1 month	A booster dose should be considered in individuals at continued risk of exposure to

Age at first dose	Primary immunisation	Intervals between primary doses	Booster
Adolescents (from 11 years) and adults*			meningococcal disease, based on official recommendations [d]

[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] In case of delay, the booster should not be given later than 24 months of age.

[c] See section 5.1. The need for, and timing of, further booster doses has not yet been determined.

[d] See section 5.1.

* There are no data in adults above 50 years of age.

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.

For instructions on the handling of the vaccine before administration, see section 6.6.

4.3 Contraindications:

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

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 a 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 BEXSERO.

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). It is important that procedures are in place to avoid injury from fainting.

This vaccine should not be given to individuals with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection.

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).

Prophylactic administration of antipyretic medicines at the time and closely after vaccination can reduce the incidence and intensity of post-vaccination febrile reactions. Antipyretic medicine should be initiated according to local guidelines in infants and children (less than 2 years of age).

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 dysfunctions (see section 5.1).

Individuals with familial complement deficiencies (for example, C3 or C5 deficiencies) and individuals receiving treatment that inhibit terminal complement activation (for example, eculizumab) are at increased risk for invasive disease caused by *Neisseria meningitidis* group B, even if they develop antibodies following vaccination with BEXSERO.

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

Although no natural rubber latex is detected in the syringe tip cap, the safe use of BEXSERO in latex-sensitive individuals has not been established. Healthcare professionals should administer BEXSERO with caution to subjects with a known history of hypersensitivity to latex.

Kanamycin is used in the 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 µg per dose. The safe use of BEXSERO in kanamycin-sensitive individuals has not been established.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

Contains sucrose. BEXSERO contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take BEXSERO.

Paediatric population:

As with many vaccines, healthcare professionals should be aware that a temperature elevation may occur following vaccination of infants and children (less than 2 years of age).

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.

4.5 Interaction with other medicines and other forms of interaction:

Use with other vaccines:

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 groups A, C, W, Y conjugate.

Clinical studies demonstrated that the immune responses of the co-administered routine vaccines were unaffected by concomitant administration of BEXSERO, based on non-inferior antibody response rates to the routine vaccines given alone. Inconsistent results were seen across studies for responses to inactivated poliovirus type 2 and pneumococcal conjugate serotype 6B and lower antibody titers to the pertussis pertactin antigen were also noted, but these data do not suggest clinically significant interference.

Due to an increased risk of fever, tenderness at the injection site, change in eating habits and irritability when BEXSERO was co-administered with the above vaccines, separate vaccinations can be considered when possible. 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. Administration of vaccines containing whole cell pertussis concomitantly with BEXSERO has not been studied and is therefore not recommended.

When given concomitantly with other vaccines, BEXSERO must be administered at separate injection sites (see section 4.2).

4.6 Fertility, pregnancy and lactation:

Pregnancy:

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.

There was no evidence of maternal or fetal toxicity and no effects on pregnancy, maternal behaviour, female fertility, or postnatal development in a study in which female rabbits received BEXSERO at approximately 10 times the human dose equivalent based on body weights.

Breastfeeding:

Information on the safety of BEXSERO to women and their children during breastfeeding is not available.

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 antibodies were detected in the offspring, but antibody levels in milk were not determined.

Fertility:

There is no data on fertility in humans.

There were no effects on female fertility in animal studies.

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 undesirable effects mentioned under section 4.8 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 17 studies including 10 randomised controlled clinical trials with 10 565 subjects (from 2 months of age) who received at least one dose of BEXSERO. Among BEXSERO recipients, 6 837 were infants and children (less than 2 years of age), 1 051 were children (2 to 10 years of age) and 2 677 were adolescents and adults.

Of the subjects who received primary infant series of BEXSERO, 3 285 received a booster dose in the second year of life.

In infants and children (less than 2 years of age) 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 vaccinated at 2, 4 and 6 months of age, fever (≥ 38 °C) was reported by 69 % to 79 % of subjects 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) compared with 44 % to 59 % of subjects receiving the routine vaccines 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.

Tabulated list of adverse reactions:

Clinical trial data:

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.

Table 2. Infants and children (up to 10 years of age):

Body system category	Frequency	Adverse event
Metabolism and nutrition disorders	Very common	Eating disorders
Nervous system disorders	Very common Uncommon	Sleepiness, unusual crying, headache Seizures
Vascular disorders	Uncommon Rare	Pallor (rare after booster) Kawasaki syndrome
Gastrointestinal disorders	Very common	Diarrhoea, vomiting (uncommon after booster)
Skin and subcutaneous tissue disorders	Very common Common Uncommon Rare	Rash (children aged 12 to 23 months) (uncommon after booster) Rash (infants and children 2 to 10 years of age) Eczema Urticaria
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
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
	Uncommon	Fever (≥ 40 °C)

Table 3. Adolescents (from 11 years of age) and adults:

Body system category	Frequency	Adverse event
Nervous system disorders	Very common	Headache
Gastrointestinal disorders	Very common	Nausea
Musculoskeletal and connective tissue disorders	Very common	Myalgia, arthralgia
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

Post-marketing data:

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

Blood and lymphatic system disorders: lymphadenopathy

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)

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).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of BEXSERO is important. It allows continued monitoring of the benefit/risk balance of BEXSERO. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the ***6.04 Adverse Drug Reactions Reporting Form***, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

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

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Category: 30.2 Antigens

Pharmacotherapeutic group: meningococcal vaccines, ATC code: J07AH09

Mechanism of action:

Immunisation with BEXSERO is intended to stimulate the production of bactericidal antibodies that recognise the vaccine antigens NHBA, NadA, fHbp, and PorA P1.4 (the immunodominant antigen present in the OMV component) and are expected to be protective against invasive meningococcal disease (IMD). As these antigens are variably expressed by different strains, meningococci that express them at sufficient levels are susceptible to killing by vaccine-elicited antibodies. The meningococcal antigen typing system (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) and ultimately to predict breadth of strain coverage.

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:

The efficacy of BEXSERO has not been evaluated through clinical trials. Vaccine efficacy has been inferred by demonstrating the induction of serum bactericidal antibody responses to each of the vaccine antigens (see section *Immunogenicity*)..

Data generated in real-world settings:

Impact of vaccination on disease incidence:

In the UK, BEXSERO was introduced into the national immunisation program (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 (PHE) conducted a 3-year observational study at the national level covering the entire birth cohort. After three years of the program, a statistically significant reduction of 75 % [incidence rate ratio (IRR) 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.

The European Medicines Agency has deferred the obligation to submit the results of studies with BEXSERO in one or more subsets of the paediatric population in the prevention of meningococcal disease caused by *Neisseria meningitidis* group B (see section 4.2 for information on paediatric use).

Immunogenicity:

Serum bactericidal antibody responses to each of the vaccine antigens NadA, fHbp, NHBA and PorA P1.4 were evaluated using a set of four meningococcal group B reference strains. Bactericidal antibodies against these strains were measured by the serum bactericidal assay using human serum as the source of complement (hSBA). Data are not available from all vaccine schedules using the reference strain for NHBA.

Most of the primary immunogenicity studies were conducted as randomised, controlled, multicenter, clinical trials. Immunogenicity was evaluated in infants, children, adolescents and adults.

Immunogenicity in infants and children:

In infant studies, participants received three doses of BEXSERO either at 2, 4 and 6 or 2, 3 and 4 months of age and a booster dose in their second year of life, as early as 12 months of age. Sera were obtained both before vaccination, one month after the third vaccination (see Table 4) and one month after booster vaccination (see Table 5). In an extension study the persistence of the immune response was assessed one year after the booster dose (see Table 5). Previously unvaccinated children also received two doses in the second year of life, with antibody persistence being measured at one year after the second dose (see Table 6). The immunogenicity after two doses has been also documented in another study in infants 6 months to 8 months of age at enrolment (see Table 6).

A two-dose schedule followed by a booster has been evaluated in infants 3 months to 5 months of age in a clinical study.

Immunogenicity in infants 2 months to 5 months of age:

Three-dose primary series followed by a booster:

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 4. Bactericidal antibody responses one month after the third vaccination against meningococcal reference strains were high against the fHbp, NadA and PorA P1.4 antigens at both BEXSERO vaccination schedules. The bactericidal responses against the NHBA antigen were also high in infants vaccinated at the 2, 4, 6-month schedule, but this antigen appeared to be less immunogenic at the 2, 3, 4-month schedule. The clinical consequences of the reduced immunogenicity of the NHBA antigen at this schedule are not known.

Table 4. Serum bactericidal antibody responses at 1 month following the third dose of BEXSERO given at 2, 3, 4 or 2, 4, 6 months of age:

Antigen		**Study V72P13** **2, 4, 6 months**	**Study V72P12** **2, 3, 4 months**	**Study V72P16** **2, 3, 4 months**
fHbp	% seropositive* (95 % CI)	N = 1149 100 % (99-100)	N = 273 99 % (97-100)	N = 170 100 % (98-100)
	hSBA GMT** (95 % CI)	91 (87-95)	82 (75-91)	101 (90-113)
NadA	% seropositive (95 % CI)	N = 1152 100 % (99-100)	N = 275 100 % (99-100)	N = 165 99 % (97-100)
	hSBA GMT (95 % CI)	635 (606-665)	325 (292-362)	396 (348-450)
PorA P1.4	% seropositive (95 % CI)	N = 1152 84 % (82-86)	N = 274 81 % (76-86)	N = 171 78 % (71-84)
	hSBA GMT (95 % CI)	14 (13-15)	11 (9,14-12)	10 (8,59-12)
NHBA	% seropositive (95 % CI)	N = 100 84 % (75-91)	N = 112 37 % (28-46)	N = 35 43 % (26-61)
	hSBA GMT (95 % CI)	16 (13-21)	3, 24 (2,49-4,21)	3, 29 (1,85-5,83)

* % seropositive = the percentage of subjects who achieved an hSBA ≥ 1:5.

** GMT = geometric mean titer.

Data on bactericidal antibody persistence at 8 months after BEXSERO vaccination at 2, 3 and 4 months of age, and at 6 months after BEXSERO vaccination at 2, 4 and 6 months of age (pre-booster time point) and booster data after a fourth dose of BEXSERO administered at 12 months of age are summarised in Table 5. Persistence of the immune response one year after the booster dose is also presented in Table 5.

Table 5. Serum bactericidal antibody responses following a booster at 12 months of age after a primary series administered at 2, 3 and 4 or 2, 4 and 6 months of age, and persistence of bactericidal antibody one year after the booster:

Antigen		2, 3, 4, 12 months	2, 4, 6, 12 months
fHbp	pre-booster* % seropositive** (95 % CI) hSBA GMT*** (95 % CI)	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 (95 % CI) hSBA GMT (95 % CI)	N = 83 100 % (96-100) 135 (108-170)	N = 422 100 % (99-100) 128 (118-139)
	12 months after booster % seropositive (95 % CI) hSBA GMT (95 % CI)	-	N = 299 62 % (56-67) 6,5 (5,63-7,5)
NadA	pre-booster % seropositive (95 % CI) hSBA GMT (95 % CI)	N = 79 97 % (91-100) 63 (49-83)	N = 423 99 % (97-100) 81 (74-89)
	1 month after booster % seropositive (95 % CI) hSBA GMT (95 % CI)	N = 84 100 % (96-100) 1 558 (1 262-1 923)	N = 421 100 % (99-100) 1 465 (1 350-1 590)
	12 months after booster % seropositive (95 % CI) hSBA GMT (95 % CI)	-	N = 298 97 % (95-99) 81 (71-94)
PorA P1.4	pre-booster % seropositive (95 % CI) hSBA GMT (95 % CI)	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 (95 % CI) hSBA GMT (95 % CI)	N = 86 97 % (90-99) 47 (36-62)	N = 424 95 % (93-97) 35 (31-39)
	12 months after booster % seropositive (95 % CI) hSBA GMT (95 % CI)	-	N = 300 17 % (13-22) 1,91 (1,7-2,15)
NHBA	pre-booster % seropositive (95 % CI) hSBA GMT (95 % CI)	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 (95% CI) hSBA GMT (95% CI)	N = 67 76 % (64-86) 12 (8,52-17)	N = 100 98 % (93-100) 42 (36-50)
	12 months after booster % seropositive (95 % CI) hSBA GMT (95 % CI)	-	N = 291 36 % (31-42) 3,35 (2,88-3,9)

*	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 subjects who achieved an hSBA ≥ 1:5.
***	GMT = geometric mean titer.

A decline in antibody titers to PorA P1.4 and fHbp antigens (reaching 9 % - 10 % and 12 % - 20 % of subjects with an hSBA ≥ 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 ≥ 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 series followed by a booster*:*

The immunogenicity after two primary doses (at 3 and a half and 5 months of age) or three primary doses (at 2 and a half, 3 and a half and 5 months of age) of BEXSERO followed by a booster dose in infants starting vaccination between 2 and 5 months of age has been evaluated in an additional phase 3 clinical study. The percentages of seropositive subjects (i.e., achieving an hSBA of at least 1:4) 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 subjects 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. Comparable percentages of subjects were seropositive at 2 to 3 years after being previously vaccinated with either two doses followed by a booster of BEXSERO (ranging from 35 % to 91 %) or three doses followed by a booster (ranging from 36 % to 84 %). In the same study the response to an additional dose administered 2 to 3 years after the booster was indicative

of immunological memory as shown by a robust antibody response against all 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 to 11 months and children 12 to 23 months of age:

The immunogenicity after two doses administered two months apart in children 6 months to 23 months of age has been documented in two studies whose results are summarised in Table 6. Against each of the vaccine antigens, seroresponse rates and hSBA GMTs were high and similar after the two-dose series in infants 6-8 months of age and children 13-15 months of age. Data on antibody persistence one year after the two doses at 13 and 15 months of age are also summarised in Table 6.

Table 6. Serum bactericidal antibody responses following BEXSERO vaccination at 6 and 8 months of age or 13 and 15 months of age and persistence of bactericidal antibody one year after the two doses at 13 and 15 months of age:

Antigen		**Age range**	
		6 to 11 months of age	**12 to 23 months of age**
		Age of vaccination	
		6, 8 months	**13, 15 months**
fHbp	1 month after 2nd dose	N = 23	N = 163
	% seropositive* (95 % CI)	100 % (85-100)	100 % (98-100)
	hSBA GMT** (95 % CI)	250 (173-361)	271 (237-310)
	12 months after 2nd dose	-	N = 68
	% seropositive (95 % CI)	-	74 % (61-83)
	hSBA GMT (95 % CI)	-	14 (9,4-20)
NadA	1 month after 2nd dose	N = 23	N = 164
	% seropositive (95 % CI)	100 % (85-100)	100 % (98-100)
	hSBA GMT (95 % CI)	534 (395-721)	599 (520-690)
	12 months after 2nd dose	-	N = 68
	% seropositive (95 % CI)	-	97 % (90-100)
	hSBA GMT (95% CI)	-	70 (47-104)

PorA P1.4	1 month after 2nd dose	N = 22	N = 164
	% seropositive (95 % CI)	95 % (77-100)	100 % (98-100)
	hSBA GMT (95 % CI)	27 (21-36)	43 (38-49)
	12 months after 2nd dose	-	N = 68
	% seropositive (95 % CI)	-	18 % (9-29)
	hSBA GMT (95 % CI)	-	1,65 (1,2-2,28)
NHBA	1 month after 2nd dose	-	N = 46
	% seropositive (95 % CI)	-	63 % (48-77)
	hSBA GMT (95 % CI)	-	11 (7,07-16)
	12 months after 2nd dose	-	N = 65
	% seropositive (95 % CI)	-	38 % (27-51)
	hSBA GMT (95 % CI)	-	3,7 (2,15-6,35)
* % seropositive = the percentage of subjects who achieved an hSBA ≥ 1:4 (in the 6 to 11 months range of age) and an hSBA ≥ 1:5 (in the 12 to 23 months range of age). ** GMT = geometric mean titer.			

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 an initial phase 3 clinical study and its extension. In the initial study, whose results are summarised in Table 7, 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 7).

Table 7. 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 ≥ 1:4 (against reference strains for fHbp, NadA, PorA P1.4 antigens) and an hSBA ≥ 1:5 (against reference strain for NHBA antigen).

** GMT = geometric mean titer.

In the extension study, in which two doses of BEXSERO were administered one month apart in unvaccinated children, a high percentage of subjects were seropositive one month after the second dose. 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) across strains ranged from 46 % to 95 % at one month after the first dose and from 69 % to 100 % at one month after the second dose (Table 8).

Table 8. Serum bactericidal antibody responses at 1 month following the second dose of BEXSERO given to children 2-10 years of age following a 0, 1-month schedule:

Antigen		**35 to 47 months of age**	**4 to 7 years of age**	**8 to 10 years of age**
fHbp	% seropositive* (95 % CI)	N = 98 100 % (96,3-100)	N = 54 98 % (90,1-99,95)	N = 34 100 % (89,7-100)
	hSBA GMT** (95 % CI)	107 (84-135)	76,62 (54-108)	52,32 (34-81)
NadA	% seropositive (95 % CI)	N = 98 100 % (96,3-100)	N = 54 100 % (93,4-100)	N = 34 100 % (89,7-100)
	hSBA GMT (95 % CI)	631 (503-792)	370,41 (264-519)	350,49 (228-540)

PorA P1.4	% seropositive (95 % CI)	N = 98 100 % (96,3-100)	N = 54 100 % (93,4-100)	N = 33 100 % (89,4-100)
	hSBA GMT (95 % CI)	34 (27-42)	30,99 (28-49)	30,75 (20-47)
NHBA	% seropositive (95 % CI)	N = 91 75 % (64,5-83,3)	N = 52 69 % (54,9-81,3)	N = 34 76 % (58,8-89,3)
	hSBA GMT (95 % CI)	12 (7,57-18)	9,33 (5,71-15)	12,35 (6,61-23)

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

** GMT = geometric mean titer.

The same extension study also evaluated antibody persistence and the response to a booster dose in children who received the two-dose primary series at 2-5 or 6-10 years of age. After 24-36 months, the percentages of seropositive subjects (i.e., achieving an hSBA of at least 1:4) declined, ranging across strains from 21 % to 74 % in children 4-7 years of age and from 47 % to 86 % in children 8-12 years of age. The response to a booster dose administered 24-36 months after the primary series was indicative of immunological memory as the percentages of seropositive subjects ranged across strains from 93 % to 100 % in children 4-7 years of age and from 96 % to 100 % in children 8-12 years of age.

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

Adolescents received two doses of BEXSERO with one-, two- or six-month intervals between doses; these data are summarised in Tables 9 and 10.

In studies with adults, data were obtained after two doses of BEXSERO with a one-month or two-month interval between doses (see Table 11).

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

Table 9. Serum bactericidal antibody responses in adolescents one month after 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		0, 1 months	0, 2 months	0, 6 months
fHbp	1 month after 2nd dose	N = 638	N = 319	N = 86
	% seropositive* (95% CI)	100 % (99-100)	100 % (99-100)	100 % (99-100)
	hSBA GMT** (95 % CI)	210 (193-229)	234 (209-263)	218 (157-302)
	18-23 months after 2nd dose	N = 102	N = 106	N = 49
	% seropositive (95 % CI)	82 % (74-89)	81 % (72-88)	84 % (70-93)
	hSBA GMT (95 % CI)	29 (20-42)	34 (24-49)	27 (16-45)
NadA	1 month after 2nd dose	N = 639	N = 320	N = 86
	% seropositive (95% CI)	100 % (99-100)	99 % (98-100)	99 % (94-100)
	hSBA GMT (95% CI)	490 (455-528)	734 (653-825)	880 (675-1147)
	18-23 months after 2nd dose	N = 102	N = 106	N = 49
	% seropositive (95 % CI)	93 % (86-97)	95 % (89-98)	94 % (83-99)
	hSBA GMT (95 % CI)	40 (30-54)	43 (33-58)	65 (43-98)
PorA P1.4	1 month after 2nd dose	N = 639	N = 319	N = 86
	% seropositive (95 % CI)	100 % (99-100)	100 % (99-100)	100 % (96-100)
	hSBA GMT (95 % CI)	92 (84-102)	123 (107-142)	140 (101-195)
	18-23 months after 2nd dose	N = 102	N = 106	N = 49
	% seropositive (95 % CI)	75 % (65-83)	75 % (66-83)	86 % (73-94)
	hSBA GMT (95 % CI)	17 (12-24)	19 (14-27)	27 (17-43)
NHBA	1 month after 2nd dose	N = 46	N = 46	-

Antigen		0, 1 months	0, 2 months	0, 6 months
	% seropositive (95 % CI)	100 % (92-100)	100 % (92-100)	-
	hSBA GMT (95 % CI)	99 (76-129)	107 (82-140)	-
* % seropositive = the percentage of subjects who achieved an hSBA ≥ 1:4. ** GMT = geometric mean titer.				

In the study in adolescents, bactericidal responses following two doses of BEXSERO were stratified by baseline hSBA less than 1:4 or equal to or greater than 1:4. Seroresponse rates and percentages of subjects with at least a 4-fold increase in hSBA titer from baseline to one month after the second dose of BEXSERO are summarised in Table 10. Following BEXSERO vaccination, a high percentage of subjects were seropositive and achieved 4-fold increases in hSBA titers independent of pre-vaccination status.

Table 10. Percentage of adolescents with seroresponse and at least 4-fold rise in bactericidal titers one month after two doses of BEXSERO administered according to different two-dose schedules - stratified by pre-vaccination titers:

Antigen			0, 1 months	0, 2 months	0, 6 months
fHbp	% seropositive* after 2nd dose (95 % CI)	pre-vaccination titer < 1:4	N = 369 100 % (98-100)	N = 179 100 % (98-100)	N = 55 100 % (94-100)
		pre-vaccination titer ≥ 1:4	N = 269 100 % (99-100)	N = 140 100 % (97-100)	N = 31 100 % (89-100)
	% 4-fold increase after 2nd dose (95 % CI)	pre-vaccination titer < 1:4	N = 369 100 % (98-100)	N = 179 100 % (98-100)	N = 55 100 % (94-100)
		pre-vaccination titer ≥ 1:4	N = 268 90 % (86-93)	N = 140 86 % (80-92)	N = 31 90 % (74-98)
NadA	% seropositive after 2nd dose (95 % CI)	pre-vaccination titer < 1:4	N = 427 100 % (99-100)	N = 211 99 % (97-100)	N = 64 98 % (92-100)
		pre-vaccination titer ≥ 1:4	N = 212 100 % (98-100)	N = 109 100 % (97-100)	N = 22 100 % (85-100)

Antigen			0, 1 months	0, 2 months	0, 6 months
	% 4-fold increase after 2nd dose (95 % CI)	pre-vaccination titer < 1:4	N = 426 99 % (98-100)	N = 211 99 % (97-100)	N = 64 98 % (92-100)
		pre-vaccination titer ≥ 1:4	N = 212 96 % (93-98)	N = 109 95 % (90-98)	N = 22 95 % (77-100)
PorA P1.4	% seropositive after 2nd dose (95 % CI)	pre-vaccination titer < 1:4	N = 427 100 % (98-100)	N = 208 100 % (98-100)	N = 64 100 % (94-100)
		pre-vaccination titer ≥ 1:4	N = 212 100 % (98-100)	N = 111 100 % (97-100)	N = 22 100 % (85-100)
	% 4-fold increase after 2nd dose (95% CI)	pre-vaccination titer < 1:4	N = 426 99 % (98-100)	N = 208 100 % (98-100)	N = 64 100 % (94-100)
		pre-vaccination titer ≥ 1:4	N = 211 81 % (75-86)	N = 111 77 % (68-84)	N = 22 82 % (60-95)
NHBA	% seropositive after 2nd dose (95 % CI)	pre-vaccination titer < 1:4	N = 2 100 % (16-100)	N = 9 100 % (66-100)	-
		pre-vaccination titer ≥ 1:4	N = 44 100 % (92-100)	N = 37 100 % (91-100)	-
	% 4-fold increase after 2nd dose (95 % CI)	pre-vaccination titer < 1:4	N = 2 100 % (16-100)	N = 9 89 % (52-100)	-
		pre-vaccination titer ≥ 1:4	N = 44 30 % (17-45)	N = 37 19 % (8-35)	-

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

Antibody persistence data for the study in adolescents were obtained in an extension phase 3 study. At approximately 7,5 years after the two-dose primary series, the percentages of subjects with hSBA ≥ 1:4 declined, ranging across strains from 29 % to 84 %. The response to a booster dose administered 7,5 years after the primary series was indicative of immunological memory as the percentages of subjects reaching an hSBA ≥ 1:4 across strains ranged from 93 % to 100 %.

The same study also evaluated antibody persistence data from an additional phase 3 initial study in adolescents. At approximately 4 years after the two-dose primary series, the percentages of subjects with hSBA ≥ 1:5 generally declined from a range across strains of 68 % to 100 % after the second dose to a range across strains of 9 % to 84 %. The response to a booster dose administered 4 years after the primary series was indicative of immunological memory as the percentages of subjects with hSBA ≥ 1:5 ranged across strains from 92 % to 100 %.

Table 11. Serum bactericidal antibody responses in adults after two doses of BEXSERO administered according to different two-dose schedules:

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

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

** GMT = geometric mean titer.

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 through 17 years of age with complement deficiencies (40), with asplenia or splenic dysfunction (107), and age-matched healthy subjects (85) received two doses of BEXSERO two months apart. At 1 month following the 2-dose vaccination course, the percentage of subjects 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 subjects. The percentage of healthy subjects with hSBA ≥ 1:5 was 98 % for antigen fHbp, 99 % for antigen NadA, 83 % for antigen PorA P1.4, and 99 % for antigen NHBA.

5.2 Pharmacokinetic properties:

Not applicable.

5.3 Preclinical safety data:

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

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Sodium chloride

Histidine

Sucrose

Water for injection

For adsorbent, see section 2.

6.2 Incompatibilities:

In the absence of compatibility studies, BEXSERO must not be mixed with other medicines.

6.3 Shelf life:

48 months

6.4 Special precautions for storage:

Store in a refrigerator (+2 °C to +8 °C).

Do not freeze.

Store in the original package to protect from light.

6.5 Nature and contents of container:

0,5 mL of suspension in a pre-filled syringe (Type I glass) with a plunger stopper (Type I butyl rubber) and with a rubber tip cap.

The tip cap and rubber plunger stopper of the pre-filled syringe are not made with natural rubber latex.

Pack sizes of 1 or 10 syringes, with or without needles. Not all pack sizes may be marketed.

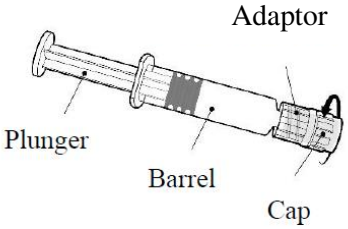
6.6 Special precautions for disposal and other handling:

Upon storage a fine off-white deposit may be observed in the pre-filled syringe containing the suspension.

Before use, the pre-filled syringe should be well shaken to form a homogeneous suspension.

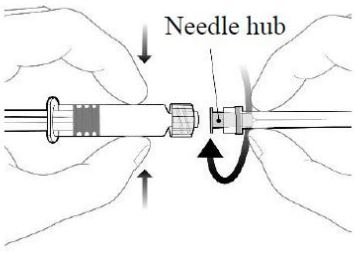
The vaccine should be visually inspected for particulate matter and discoloration prior to administration. In the event of any foreign particulate matter and/or variation of physical aspect being observed, do not administer the vaccine. If two needles of different lengths are provided in the pack, choose the appropriate needle to ensure an intramuscular administration.

Instructions for the pre-filled syringe:



Hold the syringe by the barrel, not by the plunger.

Unscrew the syringe cap by twisting it anticlockwise.



To attach the needle, connect the hub to the Adaptor and rotate a quarter turn clockwise until you feel it lock.

Do not pull the syringe plunger out of the barrel. If it happens, do not administer the vaccine.

Disposal:

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

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Limited

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8. REGISTRATION NUMBER:

54/30.2/0803

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION:

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