Bexsero Vaccine

1. NAME OF THE MEDICINAL PRODUCT

Bexsero suspension for injection in pre-filled syringe.
Multicomponent Meningococcal group B Vaccine (recombinant, adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 mL) contains:

Recombinant *Neisseria meningitidis* group B NHBA fusion protein [1, 2, 3] 50 micrograms
Recombinant *Neisseria meningitidis* group B NadA protein [1, 2, 3] 50 micrograms
Recombinant *Neisseria meningitidis* group B fHbp fusion protein [1, 2, 3] 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
[2]Adsorbed on aluminium hydroxide (0.5 mg Al^{3+})
[3]NHBA (Neisserial Heparin Binding Antigen), NadA (*Neisseria* adhesin A), fHbp (factor H binding protein)

3. PHARMACEUTICAL FORM

Suspension for injection in pre-filled syringe.
The vaccine is a 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 (see "Pharmacodynamic effects" 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

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 in the second year of life with an interval of at least 6 months between the primary series and booster dose [b]
	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 [b]
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 [b]
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 meningococcal disease, based on official recommendations [b]
Adolescents (from 11 years) and adults*			

[a] The safety and efficacy of Bexsero in infants less than 8 weeks of age has not yet been established. No data are available.

[b] See “Pharmacodynamic effects”.

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

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

Method of Administration

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

Separate injection sites must be used if more than one vaccine is administered at the same time.

For instruction on handling Bexsero before administration, see "Use and Handling".

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in sections "Formulation and Strength" and "Excipients".

4.4 Special warnings and precautions for use

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

The vaccine must not be injected intravascularly, subcutaneously or intradermally.

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

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection (see "Adverse Reactions"). 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 "Pharmacodynamic effects").

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). 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 children (less than 2 years of age).

Individuals with impaired immune responsiveness, whether due to the use of immuno-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 "Immunogenicity").

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

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

There are limited data in patients with chronic medical conditions.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h 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.

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

4.5 Interaction with other medicinal products 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. 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.
Administration of vaccines containing whole cell pertussis concomitantly with Bexsero has not been studied and thus is not recommended.

When given concomitantly with other vaccines Bexsero must be administered at separate injection sites (see "Method of Administration").

4.6 Fertility, pregnancy and lactation

There are no data on fertility in humans.
There were no effects on female fertility in animal studies.
There were no effects on the mating performance or fertility of female rabbits in an embryofoetal and developmental toxicity study in which rabbits were intramuscularly injected with Bexsero 35, 21, and 7 days prior to mating and on gestation days 7 and 20. Male fertility has not been assessed in animals.

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 foetal 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.

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

4.7 Effects on ability to drive and use machines

Bexsero has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under "Adverse Reactions" may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Clinical trial data

The safety of Bexsero was evaluated in 13 studies including 9 randomised controlled clinical trials with 7802 subjects (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 children (less than 2 years of age), 250 were children (2 to 10 years of age) and 2677 were adolescents and adults. Of the subjects who received primary infant series of Bexsero, 3285 received a booster dose in the second year of life. Data for 988 infants and children (less than 2 years of age) and 801 children (2 to 10 years of age) exposed to Bexsero in subsequent studies have additionally been evaluated. The safety of Bexsero was also evaluated in a randomised, controlled, observer-blind trial with 1803 subjects (10 to 25 years of age) who received at least one dose of Bexsero.

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.

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	≥1/1000 to <1/100
Rare	≥1/10000 to <1/1000
Very rare	<1/10000

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

Infants and children (up to 10 years of age)

Metabolism and nutrition disorders
Very common: eating disorders

Nervous system disorders
Very common: sleepiness, unusual crying, headache
Uncommon: seizures (including febrile seizures)

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

Gastrointestinal disorders
Very common: diarrhoea, vomiting (uncommon after booster)

Skin and subcutaneous tissue disorders
Very common: rash (children aged 12 to 23 months) (uncommon after booster)
Common: rash (infants and children 2 to 10 years of age)
Uncommon: eczema
Rare: 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)

Adolescents (from 11 years of age) and adults

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 listed below. Because 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)

To report any side effect(s):

Kingdom of Saudi Arabia
-National Pharmacovigilance centre (NPC)

- Reporting hotline: 19999

- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa

-GSK - Head Office, Jeddah

- Tel: +966-12-6536666
- Mobile: +966-56-904-9882
- Email: saudi.safety@gsk.com
- Website: https://gskpro.com/en-sa/
- P.O. Box 55850, Jeddah 21544, Saudi Arabia

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

ATC code

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. Bactericidal antibodies are measured by the serum bactericidal assay using human serum as the source of complement (hSBA). 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 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 (see “Data generated in real-world settings”).

Pharmacodynamic effects

Clinical efficacy

The efficacy of Bexsero has not been directly 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 "Immunogenicity"). Immunological vaccine effectiveness has been demonstrated using endogenous complement hSBA (enc-hSBA) against a broad panel of 110 diverse *Neisseria meningitidis* serogroup B strains (see "Immunological vaccine effectiveness"). Vaccine effectiveness and impact have been demonstrated in real-world settings (see "Data generated in real-world settings").

Data generated from clinical trials

Immunological vaccine effectiveness

In a clinical trial, the immunological vaccine effectiveness of Bexsero was measured by a bactericidal assay using the intrinsic complement present in the serum of each vaccine recipient (endogenous complement hSBA, enc-hSBA). This assay captures the bactericidal effect of the combined antibody responses elicited by all serogroup B meningococcal vaccine antigens and enables the assessment of the protection versus a broad panel of 110 diverse *Neisseria meningitidis* serogroup B disease-causing strains. This panel represents approximately 89% of the MenB isolates circulating worldwide from 2000-2018, ranging from 87% for European isolates to ≥90% of the isolates in Canada, U.S. and Australia. In addition, the panel included strains with a genetic profile comparable to that of the hypervirulent clusters frequently associated with outbreaks and epidemic disease.

The immunological effectiveness of Bexsero was evaluated in a phase 3, randomised, controlled, observer-blind, trial in individuals aged 10 through 25 years randomised to receive two doses of Bexsero using a 0, 2-month schedule (n=839) or a 0, 6-month schedule (n=815), or a single dose of GSK MenACWY vaccine as a control (n=172), one month after the last administered dose.

Test-based immunological vaccine effectiveness, based on the ratio between the percentages of samples lacking bactericidal activity against the panel of 110 *Neisseria meningitidis* group B invasive disease strains in participants who received two doses of Bexsero 2 or 6 months apart and in participants receiving a single dose of GSK MenACWY vaccine, is presented in Table 1.

Table 1. Immunological vaccine effectiveness (test-based) following two doses of Bexsero administered 2 or 6 months apart in participants aged 10 through 25 years

Group	Number of samples	Number of samples without bactericidal serum activity	% of samples without bactericidal serum activity	RR (97.5% CI)	Immunological vaccine effectiveness* (97.5% CI)
Bexsero 0, 2 months	27569	4648	17	0.21 (0.20-0.23)	79 (77**-80)
GSK MenACWY	4374	3456	79		
Bexsero 0, 6 months	26142	3777	14	0.18 (0.17-0.20)	82 (80**-83)
GSK MenACWY	4374	3456	79		

Study V72_72.
Abbreviations: CI = Confidence interval; RR = Relative Risk.
* Immunological vaccine effectiveness is defined as 1- RR = (1- percentage of samples without bactericidal serum activity measured by enc-hSBA in the Bexsero group / percentage of samples without bactericidal serum activity in the GSK MenACWY group) x 100%.
** Pre-specified criterion met.

Responder-based immunological vaccine effectiveness assesses the percentages of participants whose serum kills ≥70% of the tested strains. At one month after the second dose, the responder-based immunological effectiveness in participants receiving two doses of Bexsero 2 months apart was 85% (97.5% CI: 82%-88%) and 90% (97.5% CI: 87%-92%) in those receiving doses 6 months apart.

The predefined success criterion (lower limit of the 2-sided 97.5% CI for immunological vaccine effectiveness >65%) was met for both endpoints with both dosing schedules.

Data generated in real-world settings

Vaccine effectiveness

A matched case-control study on IMD prevention was conducted with Bexsero in Portugal between October 2014 and March 2019 in infants, children, and adolescents up to 18 years of age. The study showed a 79% statistically significant vaccine effectiveness [Odds Ratio 0.21 (95% CI: 0.08-0.55)] against IMD caused by *Neisseria meningitidis* group B (MenB IMD) in individuals fully vaccinated for age based on the recommendations of the Portuguese Society of Paediatrics.

Impact of vaccination on disease incidence

In the UK, Bexsero was introduced into the national immunisation programme (NIP) in September 2015 using a two-dose schedule in infants (at 2 and 4 months of age) followed by a booster dose (at 12 months of age). In this context, Public Health England (PHE) conducted a 3-year observational study at the national level covering the entire birth cohort.
After three years of the programme, a statistically significant reduction of 75% [Incidence Rate Ratio (IRR) 0.25 (95% CI: 0.19-0.36)] in MenB IMD cases was observed in vaccine-eligible infants, irrespective of the infants' vaccination status or predicted meningococcal group B strain coverage.
PHE also estimated the direct impact of Bexsero on *Neisseria meningitidis* group W IMD (MenW IMD) in birth cohorts fully eligible for Bexsero. In the four years from September 2015 to August 2019, a statistically significant reduction of 69% [IRR 0.31 (95% CI 0.20-0.67)] in MenW IMD cases was observed on top of the indirect (herd) protection provided through an existing meningococcal ACWY vaccination programme in adolescents.

In South Australia, vaccination impact data were generated from a large-scale trial conducted between January 2017 and June 2019 in high school students 16 through 19 years of age. Participants received two doses of Bexsero with a one- to three-month interval. A statistically significant reduction of 71% (95% CI: 15-90) in MenB IMD cases was observed in the two years from July 2017 to June 2019.

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. The immune response of Bexsero was assessed by measuring the production of bactericidal antibodies against each of the vaccine antigens, using the serum bactericidal activity (SBA) assay with human serum as the source of exogenous 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, multicentre, 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 (Table 2) and one month after booster vaccination (Table 3). In an extension study the persistence of the immune response was assessed one year after the booster dose (Table 3). The immunogenicity after two or three doses followed by a booster has been evaluated in infants 2 months to 5 months of age in another clinical study. The immunogenicity after two doses has been also documented in another study in infants 6 months to 8 months of age at enrolment (Table 4).

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 (Table 4).

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 2. 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 2. 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,**	**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-	N=275 100% (99-100)	N=165 99% (97-
	hSBA GMT	635 (606-665)	325 (292-362)	396 (348-450)
PorA P1.4	% seropositive (95% CI)	N=1152 84% (82-86)	N=274 81% (76-	N=171 78% (71-84)
	hSBA GMT	14 (13-15)	11 (9.14-12)	10 (8.59-12)
NHBA	% seropositive (95% CI)	N=100 84% (75-91)	N=112 37% (28-	N=35 43% (26-61)
	hSBA GMT	16 (13-21)	3.24 (2.49-	3.29 (1.85-

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

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 3. Persistence of the immune response one year after the booster dose is also presented in Table 3.

Table 3. 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) 1558 (1262-1923)	N=421 100% (99-100) 1465 (1350-1590)
	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)
	pre-booster	N=69	N=100

NHBA	% seropositive (95% CI) hSBA GMT (95% CI)	25% (15-36) 2.36 (1.75-3.18)	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 titre.

Two-dose primary series followed by a booster

The immunogenicity after two doses (at 3 and a half and 5 months of age) or three doses (at 2 and a half, 3 and a half and 5 months of age) of Bexsero followed by a booster has been evaluated in an additional phase 3 clinical study. 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 4. 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 4.

Table 4. 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 % seropositive* (95% CI) hSBA GMT** (95% CI)	N=23 100% (85-100) 250 (173-361)	N=163 100% (98-100) 271 (237-310)
	12 months after 2nd dose % seropositive (95% CI) hSBA GMT (95% CI)	-	N=68 74% (61-83) 14 (9.4-20)
NadA	1 month after 2nd dose % seropositive (95% CI) hSBA GMT (95% CI)	N=23 100% (85-100) 534 (395-721)	N=164 100% (98-100) 599 (520-690)
	12 months after 2nd dose % seropositive (95% CI) hSBA GMT (95% CI)	-	N=68 97% (90-100) 70 (47-104)
PorA P1.4	1 month after 2nd dose % seropositive (95% CI) hSBA GMT (95% CI)	N=22 95% (77-100) 27 (21-36)	N=164 100% (98-100) 43 (38-49)
	12 months after 2nd dose % seropositive (95% CI) hSBA GMT (95% CI)	-	N=68 18% (9-29) 1.65 (1.2-2.28)
NHBA	1 month after 2nd dose % seropositive (95% CI) hSBA GMT (95% CI)	-	N=46 63% (48-77) 11 (7.07-16)
	12 months after 2nd dose % seropositive (95% CI) hSBA GMT (95% CI)	-	N=65 38% (27-51) 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 titre.

The seroresponse rates were 98% to 100% against all strains following a booster dose given at approximately one year after the administration of two doses at 13 and 15 months of age.

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 5, participants received two doses of Bexsero two months apart. The seroresponse rates and hSBA GMTs were high after the two-dose schedule in children against each of the vaccine antigens (Table 5).

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

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

* % seropositive = the percentage of subjects who achieved an hSBA ≥ 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 titre.

In the extension study, in which two doses of Bexsero were administered one month apart in unvaccinated children, high percentages 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.

This 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 6 and 7. As early as one month post- vaccination with the first dose, percentages of subjects who achieved an hSBA ≥ 1:4 ranged from 90% to 97% (Table 6).

In studies with adults, data were obtained after two doses of Bexsero with a one month or two-month interval between doses (Table 8).

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 6. 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		**0, 1 months**	**0, 2months**	**0, 6months**
fHbp	1 month after 1st dose	N=677	N=342	N=112
	% seropositive* (95% CI)	94% (92-96)	92% (88-94)	92% (85-96)
	hSBA GMT** (95% CI)	60 (53-69)	52 (43-63)	46 (33-63)
	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 1st dose	N=677	N=342	N=111
	% seropositive (95% CI)	97% (95-98)	96% (94-98)	97% (92-99)
	hSBA GMT (95% CI)	73 (64-82)	69 (58-82)	81 (61-109)
	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 1st dose	N=677	N=342	N=111
	% seropositive (95% CI)	94% (92-96)	92% (88-94)	90% (83-95)
	hSBA GMT (95% CI)	49 (43-55)	40 (33-47)	42 (31-56)
	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	-
	% 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 titre.

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 titre from baseline to one month after the second dose of Bexsero are summarised in Table 7. Following Bexsero vaccination, a high percentage of subjects were seropositive and achieved 4-fold increases in hSBA titres independent of pre-vaccination status.

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

Antigen			0, 1 months	0, 2 months	0, 6 months
fHbp	% seropositive* after 1st dose (95% CI)	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 (95% CI)	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 (95% CI)	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 (95% CI)	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 (95% CI)	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 (95% CI)	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 (95% CI)	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 (95% CI)	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 (95% CI)	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 (95% CI)	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 (95% CI)	pre-vaccination titre <1:4	N=427 100% (98-100)	N=208 100% (98-100)	N=64 100% (94-100)
		pre-vaccination titre ≥1:4	N=212 100% (98-100)	N=111 100% (97-100)	N=22 100% (85-100)
	% 4-fold increase after 2nd dose (95% CI)	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 (95% CI)	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 (95% CI)	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)	-

* % 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 8. 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 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 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 percentages 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 percentages of healthy subjects with hSBA ≥1:5 were 98% for antigen fHbp, 99% for antigen NadA, 83% for antigen PorA P1.4, and 99% for antigen NHBA.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Component	Quantity per 0.5 mL dose	Function
Sodium chloride	3.125 mg	Tonicity adjusting agent
Sucrose	10 mg	Tonicity adjusting agent
Histidine	0.776 mg	Buffering agent
Water for Injection	up to 0.5 mL	Solvent
Aluminium hydroxide	1.5 mg	Adsorbent

Residues

Kanamycin (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)

6.2 Incompatibilities

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

6.3 Shelf life

4 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

0.5 mL of suspension in a pre-filled syringe (Type I glass) with a plunger stopper (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 pre-filled syringes, supplied with or without needles.
Not all pack sizes may be marketed.

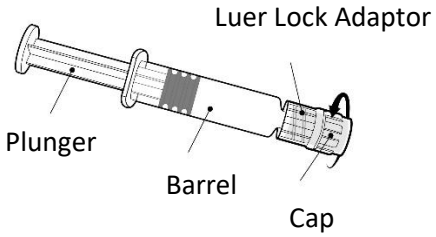
6.6 Special precautions for disposal and other handling

Upon storage of the suspension, a fine off-white deposit may form.

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

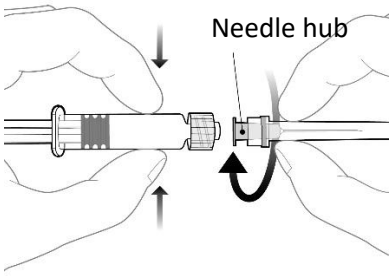
GlaxoSmithKline Saudi Arabia
Summary of product characteristics
Ref: GDSv17

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 Luer Lock 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 product or waste material should be disposed of in accordance with local requirements.

For any information about this medicinal product, please contact:
-GSK - Head Office, Jeddah

- Tel: +966-12-6536666
- Mobile: +966-56-904-9882
- Email: gcc.medinfo@gsk.com
- Website: https://gskpro.com/en-sa/
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Version number: GDSv17 / Date of issue: 11 July 2023

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