HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BEXSERO safely and effectively. See full prescribing information for BEXSERO.

BEXSERO® (Meningococcal Group B Vaccine)
Suspension for intramuscular injection
Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------

BEXSERO is a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. BEXSERO is approved for use in individuals 10 through 25 years of age. (1)

Approval of BEXSERO is based on demonstration of immune response, as measured by serum bactericidal activity against three serogroup B strains representative of prevalent strains in the United States. The effectiveness of BEXSERO against diverse serogroup B strains has not been confirmed. (1)

----------DOSAGE AND ADMINISTRATION----------

For intramuscular use only. (2)

Administer two doses (0.5 mL each) of BEXSERO at least 1 month apart. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Suspension for intramuscular injection in 0.5 mL single-dose pre-filled syringes. (3)

----------CONTRAINDICATIONS----------

Hypersensitivity, including severe allergic reaction, to any component of the vaccine, or after a previous dose of BEXSERO. (4)

----------WARNINGS AND PRECAUTIONS----------

The tip caps of the pre-filled syringes contain natural rubber latex which may cause allergic reactions in latex sensitive individuals. (5.3)

----------ADVERSE REACTIONS----------

The most common solicited adverse reactions observed in clinical trials were pain at the injection site (≥83%), myalgia (≥48%), erythema (≥45%), fatigue (≥35%), headache (≥33%), induration (≥ 28%), nausea (≥18%), and arthralgia (≥13%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

----------USE IN SPECIFIC POPULATIONS----------

- **Pregnancy:** BEXSERO should be used during pregnancy only if clearly needed. Pregnancy registry available for BEXSERO. Register women who receive BEXSERO while pregnant in the pregnancy registry by calling 1-877-413-4759. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised XX/201X

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BEXSERO® is a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. BEXSERO is approved for use in individuals 10 through 25 years of age.

Approval of BEXSERO is based on demonstration of immune response, as measured by serum bactericidal activity against three serogroup B strains representative of prevalent strains in the United States. The effectiveness of BEXSERO against diverse serogroup B strains has not been confirmed.

2 DOSAGE AND ADMINISTRATION

For intramuscular use only.

2.1 Dose and Schedule

Administer two doses (0.5 mL each) of BEXSERO at least 1 month apart.

2.2 Administration

Shake the syringe immediately before use to form a homogeneous suspension. Do not use the vaccine if it cannot be resuspended. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if particulate matter or discoloration is found.

Administer BEXSERO as a 0.5 mL intramuscular injection into the deltoid muscle of the upper arm.

2.3 Use of BEXSERO with other Meningococcal Group B Vaccines

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.

3 DOSAGE FORMS AND STRENGTHS

BEXSERO is a suspension for intramuscular injection in 0.5 mL single-dose pre-filled syringes.

4 CONTRAINDICATIONS

Hypersensitivity, including severe allergic reaction, to any component of the vaccine, or after a previous dose of BEXSERO. *[see Description (11)]*

5 WARNINGS AND PRECAUTIONS

5.1 Preventing and Managing Allergic Reactions

Appropriate observation and medical treatment should always be readily available in case of an anaphylactic event following the administration of the vaccine.

5.2 Syncope

Syncope (fainting) can occur in association with administration of BEXSERO. Ensure procedures are in place to avoid injury from falling associated with syncope.

5.3 Latex

The tip caps of the pre-filled syringes contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

5.4 Limitation of vaccine effectiveness

BEXSERO may not protect all vaccine recipients. BEXSERO may not provide protection against all meningococcal serogroup B strains *[see Clinical Pharmacology (12.1)]*.

5.5 Altered Immunocompetence

Individuals with altered immunocompetence may have reduced immune responses to BEXSERO.

6 ADVERSE REACTIONS

The most common solicited adverse reactions observed in clinical trials were pain at the injection site (≥83%), myalgia (≥48%), erythema (≥45%), fatigue (≥35%), headache (≥33%), induration (≥28%), nausea (≥18%), and arthralgia (≥13%).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

In four clinical trials, 3058 individuals 10 through 25 years of age received at least one dose of BEXSERO, 1436 participants received only BEXSERO, 2089 received only placebo or a control vaccine, and 1622 participants received a mixed regimen (placebo or control vaccine and BEXSERO).

In a randomized controlled study[1] conducted in US and Poland, 120 participants 10 through 25 years of age received at least one dose of BEXSERO, including 112 participants who received 2 doses of BEXSERO 2 months apart; 97 participants received saline placebo followed by Menveo [Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine]. Across groups, median age was 13 years, males comprised 49% and 60% were White; 34% were Hispanic, 4% were Black,<1% were Asian, and 2% were other.

In a second randomized controlled study[2] conducted in Chile, all subjects (N=1,622) 11 through 17 years of age received at least one dose of BEXSERO. This study included a subset of 810 subjects who received 2 doses of BEXSERO 1 or 2 months apart. A control group of 128 subjects received at least 1 dose of placebo containing aluminum hydroxide. A subgroup of 128 subjects received 2 doses of BEXSERO 6 months apart. In this study, median age was 14 years, males comprised 44%, and 99% were Hispanic.

In a third randomized controlled study[3] conducted in the United Kingdom (UK), 974 university students 18 through 24 years of age received at least 1 dose of BEXSERO, including 932 subjects who received 2 doses of BEXSERO 1 month apart. Comparator groups received 1

dose of Menveo followed by 1 dose of placebo containing aluminum hydroxide (N=956) or 2 doses of IXIARO (Japanese Encephalitis Vaccine, Inactivated, Adsorbed) (N=947). Across groups, median age was 20 years, males comprised 46%, and 88% were White, 5% were Asian, 2% were Black, <1% were Hispanic, and 4% were other.

In an uncontrolled study[4] conducted in Canada and Australia, 342 participants 11 through 17 years of age received at least 1 dose of BEXSERO, including 338 participants who received 2 doses of BEXSERO 1 month apart. The median age was 13 years, males comprised 55%, and 80% were White, 10% were Asian, 4% were Native American/Alaskan, and 4% were other.

Local and systemic reactogenicity data were solicited from all participants in the studies conducted in Chile, US/Poland, Canada/Australia, and in a subset of participants in the UK study. Reports of unsolicited adverse events occurring within the first 7 days after each vaccination were collected in all studies. In the US/Poland study, reports of unsolicited adverse events were collected up to one month after the second vaccination.

Reports of all serious adverse events, medically attended adverse events and adverse events leading to premature withdrawal were collected throughout the study period for the studies conducted in Chile (12 months), UK (12 months), US/Poland (8 months), and Canada/Australia (2 months).

Solicited Adverse Reactions

The reported rates of local and systemic reactions among participants 10 through 25 years of age following each dose of BEXSERO administered 2 months apart or control in the US/Polish study[1] are presented in Table 1.

Table 1: Percentage of US and Polish Participants 10 through 25 Years of Age Reporting Solicited Local and Systemic Adverse Reactions within 7 Days after BEXSERO or Control, by Dose

Solicited Reaction[a]		Dose 1		Dose 2[b]	
		BEXSERO	Placebo (Saline)	BEXSERO	Menveo
		N=110-114	N= 94-96	N=107-109	N=90-92
Local Adverse Reactions					
Pain	Any	90	27	83	43
	Mild	27	20	18	26
	Moderate	44	5	37	9
	Severe	20	2	29	8
Erythema	Any	50	13	45	26
	1-25 mm	41	11	36	13
	>25-50 mm	6	1	5	6
	>50-100 mm	3	0	5	4
	>100 mm	0	0	0	2
Induration	Any	32	10	28	23
	1-25 mm	24	9	22	16

	>25-50 mm	7	0	4	0
	> 50-100 mm	1	1	2	4
	> 100 mm	0	0	0	2
Systemic Adverse Reactions					
Fatigue	Any	37	22	35	20
	Mild	19	17	18	11
	Moderate	14	5	10	7
	Severe	4	0	6	2
Nausea	Any	19	4	18	4
	Mild	12	3	10	3
	Moderate	4	1	5	1
	Severe	4	0	4	0
Myalgia	Any	49	26	48	25
	Mild	21	20	16	14
	Moderate	16	5	19	7
	Severe	12	1	13	4
Arthralgia	Any	13	4	16	4
	Mild	9	3	8	2
	Moderate	3	1	6	2
	Severe	2	0	2	0
Headache	Any	33	20	34	23
	Mild	19	15	21	8
	Moderate	9	4	6	12
	Severe	4	1	6	3
Fever	≥38°C	1	1	5	0
	38.0-38.9°C	1	1	4	0
	39.0-39.9°C	0	0	1	0
	≥40°C	0	0	0	0

Clinicaltrials.gov Identifier NCT01272180.
[a] Erythema, and induration: Any (≥ 1 mm).Pain and systemic reactions: mild (transient with no limitation in normal daily activity); moderate (some limitation in normal daily activity); severe (unable to perform normal daily activity)
[b] Administered 2 months after Dose 1

Solicited adverse reaction rates were similar among participants 11 through 24 years of age who received BEXSERO in the other three clinical studies,[2,3,4] except for severe myalgia which was reported by 3-7% of subjects. Severe pain was reported by 8% of university students in the UK[3].

Non-serious Adverse Events

In the 3 controlled studies[1,2,3] (BEXSERO N=2221, control N=2204), non-serious unsolicited adverse events that occurred within 7 days of any dose were reported by 439 (20%) BEXSERO and 197 (9%) control recipients. Unsolicited adverse events that were reported among at least 2% of participants and were more frequently reported in BEXSERO recipients than in control recipients were injection site pain, headache, and injection site induration unresolved within 7 days, and nasopharyngitis.

Serious Adverse Events

Overall, in clinical studies, among 3,058 participants 10 through 25 years of age who received at least 1 dose of BEXSERO, 66 (2.1%) participants reported serious adverse events at any time during the study. In the 3 controlled studies[1,2,3] (BEXSERO N=2716, Control N=2078), serious adverse events within 30 days after any dose were reported in 23 (0.8%) BEXSERO recipients and 10 (0.5%) control recipients.

6.2 Additional Pre-licensure Safety Experience

In response to outbreaks of serogroup B meningococcal disease at two universities in the US, BEXSERO was administered as a 2 dose series at least 1 month apart. Information on serious adverse events was collected for a period of 30 days after each dose from 15,351 individuals 16 through 65 years of age who received at least 1 dose. Overall 50 individuals (0.3%) reported serious adverse events, including one event considered related to vaccination, a case of anaphylaxis within 30 minutes following vaccination.

6.3 Postmarketing Experience

Adverse event reports received for BEXSERO marketed outside the US are listed below. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency, or to establish a causal relationship to vaccination. This list includes serious events or events which have suspected causal association to BEXSERO.

General disorders and administration site conditions:	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), rash, eye swelling.
Nervous System Disorders:	Syncope, vasovagal responses to injection.

7 DRUG INTERACTIONS

Sufficient data are not available to establish the safety and immunogenicity of concomitant administration of BEXSERO with recommended adolescent vaccines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B:

Reproduction studies have been performed in rabbits at doses up to 15 times the human dose on a body weight basis and have revealed no evidence of impaired fertility in females or harm to the fetus due to BEXSERO. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, BEXSERO should be used during pregnancy only if clearly needed.

Pregnancy Registry for BEXSERO

GlaxoSmithKline maintains a surveillance registry to collect data on pregnancy outcomes and newborn health status outcomes following exposure to BEXSERO during pregnancy. Women who receive BEXSERO during pregnancy should be encouraged to contact GlaxoSmithKline directly or their healthcare provider should contact GlaxoSmithKline by calling 1-877-413-4759.

8.3 Nursing Mothers

It is not known whether BEXSERO is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BEXSERO is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of BEXSERO have not been established in children younger than 10 years of age.

8.5 Geriatric Use

Safety and effectiveness of BEXSERO have not been established in adults older than 65 years of age.

11 DESCRIPTION

BEXSERO (Meningococcal Group B Vaccine) is a sterile, white, opalescent, suspension for intramuscular injection. Each 0.5 mL dose of BEXSERO is formulated to contain 50 micrograms each of recombinant proteins Neisserial adhesin A (NadA), Neisserial Heparin Binding Antigen (NHBA), and factor H binding protein (fHbp), 25 micrograms of Outer Membrane Vesicles (OMV), 1.5 mg aluminum hydroxide (0.519 mg of Al^{3+}), 3.125 mg sodium chloride, 0.776 mg histidine, and 10 mg sucrose at pH 6.4 – 6.7.

The NadA component is a fragment of the full-length protein derived from *N. meningitidis* strain 2996 (peptide 8 variant 2/3)[5]. The NHBA component is a recombinant fusion protein comprised of NHBA (peptide 2)[5] and accessory protein 953 derived from *N. meningitidis* strains NZ98/254 and 2996, respectively. The fHbp component is a recombinant fusion protein comprised of fHbp (variant 1.1)[5] and the accessory protein 936 derived from *N. meningitidis* strains MC58 and 2996, respectively. These three recombinant proteins are individually produced in *Escherichia coli* and purified through a series of column chromatography steps. The OMV antigenic component is produced by fermentation of *N. meningitidis* strain NZ98/254 (expressing outer membrane protein PorA serosubtype P1.4)[6], followed by inactivation of the bacteria by deoxycholate, which also mediates vesicle formation. The antigens are adsorbed onto aluminum hydroxide.

Each dose contains less than 0.01 micrograms kanamycin (by calculation).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Protection against invasive meningococcal disease is conferred mainly by complement-mediated antibody-dependent killing of *N. meningitidis*. The effectiveness of BEXSERO was assessed by measuring serum bactericidal activity using human complement (hSBA).

NHBA, NadA, fHbp, and PorA are proteins found on the surface of meningococci and contribute to the ability of the bacterium to cause disease. Vaccination with BEXSERO leads to the production of antibodies directed against NHBA, NadA, fHbp, and PorA P1.4 (present in OMV). The susceptibility of serogroup B meningococci to complement-mediated antibody-dependent killing following vaccination with BEXSERO is dependent on both the antigenic similarity of the bacterial and vaccine antigens, as well as the amount of antigen expressed on the surface of the invading meningococci.

13 NONCLINICAL TOXICOLOGY

BEXSERO has not been evaluated for carcinogenic or mutagenic potential or impairment of male fertility.

14 CLINICAL STUDIES

The immunogenicity of BEXSERO following 2 doses was evaluated in individuals 11 through 24 years of age. Serum bactericidal antibodies were measured with hSBA assays using three strains selected to measure responses to one of three vaccine antigens, either fHbp, NadA or PorA P1.4, prevalent among strains in the US. A suitable strain for assessing bactericidal activity of NHBA-specific antibodies was not available. Studies assessed the proportion of subjects who achieved a 4-fold or greater increase in hSBA titer for each of the three strains, and the proportion of subjects with a titer greater than or equal to the lower limit of quantitation (LLOQ) of the assay for all three strains (composite response). The LLOQ was defined as the lowest amount of the antibody in a sample that can be reliably quantified. Available data showed that baseline antibody titers across populations vary.

14.1 Immunogenicity

In a clinical trial conducted in Canada and Australia, adolescents 11 through 17 years of age received two doses of BEXSERO one month apart. The hSBA responses one month after the second dose are shown in Table 2.

Table 2: Bactericidal Antibody Response Rates Following 2 Doses of BEXSERO Administered 1 Month Apart to Canadian and Australian Adolescents[a]

≥ 4-Fold hSBA Response 1 Month Post Dose 2[b,c]			
Strain (Antigen)	**N**	**%**	**95% CI**
H44/76 (fHbp)	298	98	95, 99
5/99 (NadA)	299	99	98,100
NZ98/254 (PorA P1.4)	298	39	33,44
Composite hSBA Response [c,d]			
Time point	**N**	**%**	**95% CI**
Baseline (pre-vaccination)	299	0	
1 Month Post Dose 2	298	63	57, 68

NCT 01423084
Abbreviations: CI = Confidence interval; hSBA = Serum bactericidal activity measured using human complement; LLOQ = Lower limit of quantitation
[a] Evaluable Immunogenicity Population (11 through 17 years of age)
[b] ≥ 4-fold hSBA response is defined as: a post-vaccination hSBA ≥ 1:16 for participants with pre-vaccination hSBA <1:4, a post-vaccination titer at least 4-fold the LLOQ for participants with pre-vaccination hSBA ≥1:4 but < LLOQ, and a post-vaccination 4-fold rise for participants with pre-vaccination hSBA ≥ LLOQ.
[c] LLOQ = 1:16 for H44/76; 1:16 for 5/99; 1:8 for NZ98/254.
[d] Composite hSBA Response means hSBA ≥ LLOQ for all 3 indicator Meningococcal B strains.

In a randomized, controlled clinical trial conducted in the UK among university students 18 through 24 years of age, hSBA responses in a subset of participants who received BEXSERO were measured 1 month and 11 months after the second dose (Table 3).

Table 3: Bactericidal Antibody Response Rates Following 2 Doses of BEXSERO Administered 1 Month Apart to University Students in the UK[a]

≥4-Fold hSBA Response 1 Month Post Dose 2[b, c]			
Strain (Antigen)	**N**	**%**	**95% CI**
H44/76 (fHbp)	148	78	71, 85
5/99 (NadA)	148	94	89, 97
NZ98/254 (PorA P1.4)	147	67	58, 74
Composite hSBA Response[c, d]			
Time point	**N**	**%**	**95% CI**
Baseline (pre-vaccination)	186	24	18, 30
1 Month Post Dose 2	147	88	82, 93
11 Months Post Dose 2	136	66	58, 72

NCT 01214850
Abbreviations: CI = Confidence interval; hSBA = Serum bactericidal activity measured using human complement; LLOQ = Lower limit of quantitation
[a] Evaluable Immunogenicity Population (18 through 24 years of age)
[b] ≥ 4-fold hSBA response is defined as: a post-vaccination hSBA ≥ 1:16 for participants with pre-vaccination hSBA <1:4, a post-vaccination titer at least 4-fold the LLOQ for participants with pre-vaccination hSBA ≥1:4 but < LLOQ, and a post-vaccination 4-fold rise for participants with pre-vaccination hSBA ≥ LLOQ.
[c] LLOQ = 1:16 for H44/76; 1:8 for 5/99; 1:16 for NZ98/254.
[d] Composite hSBA Response means hSBA ≥ LLOQ for all 3 indicator Meningococcal B strains.

15 REFERENCES

1. NCT01272180 (V102_03)
2. NCT00661713 (V72P10)
3. NCT01214850 (V72_29)
4. NCT01423084 (V72_41)
5. Wang X, et al. Vaccine 2011; 29:4739-4744.
6. Hosking J, et al. Clin Vaccine Immunol. 2007;14:1393-1399

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

BEXSERO is supplied as a 0.5 mL suspension in a glass pre-filled syringe. The tip caps of the pre-filled syringes contain natural rubber latex, the plungers are not made with natural rubber latex.

BEXSERO product presentations are listed in Table 4 below:

Table 4 BEXSERO Product Presentation

Presentation	Carton NDC Number	Components
Pre-filled syringe (Package of **1** syringe per carton)	58160-976-06	0.5 mL single-dose pre-filled syringe [NDC 58160-976-02]
Pre-filled syringe (Package of **10** syringes per carton)	58160-976-20	0.5 mL single-dose pre-filled syringe [NDC 58160-976-02]

16.2 Storage and Handling

Do not freeze. Discard if the vaccine has been frozen.

Store refrigerated, at 36°F to 46°F (2°C to 8°C).

Protect from light.

Do not use after the expiration date.

17 PATIENT COUNSELING INFORMATION

Provide the Vaccine Information Statement. These are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

Inform patients, parents or guardians about:

- The importance of completing the immunization series.
- Reporting any adverse reactions to their healthcare provider.
- Register women who receive BEXSERO while pregnant in the pregnancy registry by calling 1-877-413-4759. *[see Use in Specific Populations (8.1)]*

Manufactured by **GSK Vaccines, Srl**
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US License No. 1617

Distributed by **GlaxoSmithKline**
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BXS:XPI