PRODUCT MONOGRAPH

BEXSERO®

Multicomponent Meningococcal B Vaccine (recombinant, adsorbed)

BEXSERO® Suspension for Injection

Active Immunizing Agent for the Prevention of Meningococcal Disease

ATC Code: J07AH09

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular injection	Suspension for injection. White opalescent liquid suspension. Recombinant *Neisseria meningitidis* serogroup B NHBA fusion protein 50 µg [1,2,3]. Recombinant *Neisseria meningitidis* serogroup B NadA protein 50 µg [1,2,3]. Recombinant *Neisseria meningitidis* serogroup B fHbp fusion protein 50 µg [1,2,3]. Outer membrane vesicles (OMV) from *Neisseria meningitidis* serogroup B strain NZ98/254 25 µg measured as amount of total protein containing the PorA P1.4 [2]. *[1] Produced in E. coli by recombinant DNA technology.* *[2]Adsorbed on aluminum hydroxide (0.5 mg aluminum).* *[3]NHBA (Neisseria Heparin Binding Antigen), NadA (Neisserial adhesin A), fHbp (factor H binding protein).*	*For a complete listing see Dosage Forms, Composition and Packaging Section.*

DESCRIPTION

BEXSERO is a liquid vaccine that contains three purified *Neisseria meningitidis* serogroup B protein antigens: NadA (Neisserial adhesin A) as a single protein, NHBA (Neisseria Heparin Binding Antigen) as a fusion protein, fHbp (factor H Binding Protein) as a fusion protein and PorA P1.4 as the main antigen of Outer Membrane Vesicles (OMV) derived from *N. meningitidis* serogroup B, strain NZ 98/254. These antigens are adsorbed on aluminum hydroxide. The sequences of the recombinant protein antigens are derived from the following *N. meningitidis* serogroup B strains: NHBA is derived from strain NZ 98/254 and is fused with accessory protein 953 derived from strain 2996; NadA is derived from strain 2996 and fHbp is derived from strain MC58 and is fused with accessory protein 936, derived from strain 2996. The OMV antigen is a suspension that consists of small, membranous spherical vesicles, or fragments of vesicles, in which the native complex antigen composition of the subcapsular cell surface of *N. meningitidis* serogroup B, strain NZ98/254 (B:4:P1.7-2,4) is highly conserved and contains outer membrane protein PorA P1.4 as the main antigen. The recombinant proteins are prepared by recombinant DNA technology using extrachromosomal expression plasmid vectors in *Escherichia coli* cells. The OMV antigen is produced by fermentation of *N. meningitidis* strain NZ98/254, followed by inactivation of the bacteria with deoxycholate, which also mediates vesicle formation.

INDICATIONS AND CLINICAL USE

BEXSERO is indicated for active immunization of individuals from 2 months through 17 years old against invasive disease caused by *N. meningitidis* serogroup B strains.

As the expression of antigens included in the vaccine is epidemiologically variable in circulating group B strains, meningococci that express them at sufficient levels are predicted to be susceptible to killing by vaccine-elicited antibodies (see section ACTION AND CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

BEXSERO should not be administered to individuals who are hypersensitive to this vaccine or to any ingredient in the formulation or components of the container closure.
For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.

WARNINGS AND PRECAUTIONS

General

As with any vaccine, vaccination with Bexsero may not protect all vaccine recipients.
BEXSERO is not expected to provide protection against all circulating meningococcal serogroup B strains.

The vaccine antigens present in BEXSERO are also expressed by meningococci belonging to serogroups other than serogroup B. However, protection against invasive meningococcal disease (IMD) caused by other serogroups has not been studied. Therefore, protection against IMD caused by other serogroups should not be assumed.

Do not inject intravascularly.

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

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection (see section ADVERSE REACTIONS). It is important that procedures are in place to avoid injury from fainting.

There are no data on the use of BEXSERO in patients with chronic medical conditions.

As with all injectable pediatric vaccines, 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 $\leq$ 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.

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

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

Febrile Illness

As with many other vaccines, the physician should be aware that a temperature elevation may occur following vaccination of infants and children (less than 2 years of age). Prophylactic administration of acetaminophen at the time of, and closely after vaccination, can reduce the incidence and intensity of post-vaccination febrile reactions in infants and children (less than 2 years of age).
Administration of BEXSERO should be postponed in subjects suffering from an acute severe febrile illness. However, the presence of a minor infection, such a cold, should not be a reason to defer vaccination.

Hematologic

This vaccine should not be given to individuals with thrombocytopenia, hemophilia or any coagulation disorder that would contraindicate intramuscular injection, unless the potential benefit clearly outweighs the risk of administration.

Immune

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

Sexual Function/Reproduction

There are no data on fertility in humans.
No effects on fertility were observed in female rabbits receiving BEXSERO pre-mating and during pregnancy.

Special Populations

Pregnant Women:
Insufficient clinical data on exposed pregnancies are available.
The potential risk for pregnant humans is unknown. Nevertheless, vaccination should not be withheld when there is a clear risk of exposure to meningococcal infection.

Preclinical data
Based on reproductive toxicology data in rabbits, BEXSERO is not predicted to affect pregnancy and parturition, or to increase the risk of embryofetal abnormalities.

Nursing Women:
No data are available. The benefit-risk ratio must be examined before making the decision to immunise during breast-feeding.

Preclinical data
In a rabbit study, no effects on postnatal development were observed in nursing offspring of vaccinated maternal animals through day 29 of lactation.

Pediatrics (< 2 months of age):
No data are available.

Individuals (> 17 years of age)

Limited safety and immunogenicity data are available in individuals from 18 to 50 years of age. The safety and immunogenicity of BEXSERO in individuals older than 50 years have not been established.

Geriatrics (> 65 years of age):
No data are available.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The incidence and severity of any local, systemic or other reactions were generally comparable in the BEXSERO groups across all studies in adolescents and adults, and in infants and children (less than 2 years of age).
The most frequent local and systemic adverse reactions after vaccination with BEXSERO observed in clinical trials were:

- Adolescents and adults: local reactions - pain, erythema, induration;
  systemic reactions - malaise, headache, myalgia.

- Infants and children (less than 2 years of age): local reactions - tenderness, erythema, induration;
  systemic reactions - fever, irritability, unusual crying, sleepiness.

Adverse Drug Reactions in Clinical Trials

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in trials may not reflect the rates observed in practice, and should not be compared with the rates in the clinical trials of another vaccine. Adverse drug reaction information from clinical trials is useful for identifying vaccine-related adverse events and for approximating rates.

The characterization of the safety profile of BEXSERO is based on data from 8 studies, including 7 randomized controlled clinical trials with 6427 participants (from 2 months of age) who received BEXSERO.
Among BEXSERO recipients, 4843 were infants and children (less than 2 years of age), and 1584 were adolescents and adults (from 11 years of age), respectively. Of the subjects who received the primary infant series of BEXSERO, 1630 received an additional dose in the second year of life.
Data on solicited local (tenderness/pain, erythema, swelling and induration) and systemic adverse reactions (change in eating habits, sleepiness, irritability, unusual crying, vomiting, diarrhea, rash, fever ≥38°C in infants and children (less than 2 years of age); myalgia, arthralgia, nausea, malaise, headache and fever in adolescents and adults) were collected in clinical studies on the day of vaccination and for the following 6 days after vaccination (days 1-7 after

vaccination). Most reactions were of a mild to moderate nature and resolved within 48 hours after vaccination with BEXSERO.

In clinical studies in infants, when BEXSERO was given alone, the frequency of fever was comparable to that associated with concomitant use of routine infant vaccines [Pneumococcal 7-valent Conjugate Vaccine, Diphtheria CRM197 Protein (Prevnar; Pfizer) and diphtheria, tetanus, acellular pertussis, hepatitis B recombinant (adsorbed), inactivated poliomyelitis and adsorbed conjugated *Haemophilus influenzae* type b vaccine (Infanrix hexa; GlaxoSmithKline Biologicals)]. Fever occurred more frequently when BEXSERO was co-administered with routine infant vaccines. Higher rates of antipyretic use were also reported for infants vaccinated with BEXSERO and routine vaccines. When fever occurred, it generally followed a predictable pattern, with the majority resolving within 48 hours after vaccination.

Solicited Adverse Reactions

Infants and Children (less than 2 years of age)

The characterization of the safety profile of BEXSERO in the infant and children (less than 2 years of age) populations was based primarily on data from 3 studies: V72P12 and V72P13 in infants 2 months of age, and V72P13E1 in children 12 to 13 months of age. In studies V72P12 and V72P13, the main schedule investigated was a three-dose primary series of BEXSERO administered at 2, 4 and 6 months of age. A three-dose accelerated schedule given at 2, 3 and 4 months of age was also evaluated in V72P12. BEXSERO was routinely administered with infant vaccines, Infanrix hexa and Prevnar, except for one group of subjects in study V72P12 who received BEXSERO alone at 2, 4 and 6 months of age and the routine vaccines at 3, 5 and 7 months of age. In study V72P13E1, which was an extension of V72P13, subjects who previously received BEXSERO at the 2, 4, 6-month schedule received a fourth dose of BEXSERO at 12 months of age; control subjects who received only the routine infant vaccines in V72P13 (vaccine naive) were vaccinated with a two-dose catch-up schedule of BEXSERO at either 12 and 14 or 13 and 15 months of age.

Data on local and systemic reactions after vaccination of infants with BEXSERO at 2, 4 and 6 months of age are shown in Table 1 and Table 2. Most of the reactions were transient and there was no clear trend of increasing frequency with subsequent doses. The reactogenicity profile was comparable for BEXSERO administered at the 2, 3, 4-month schedule.

Fever ($\geq$ 38 °C) was more frequently reported following vaccination with BEXSERO concomitantly with routine vaccines, compared with meningococcal C conjugate vaccine (Menjugate; Novartis) with concomitant routine vaccines, or routine vaccinations only (Table 2). The onset of fever in the majority of BEXSERO recipients occurred within 6 hours of vaccination and the duration of the fever was transient, resolving within 48 hours after vaccination. This pattern was consistent for all three BEXSERO doses. There was a trend for subjects to have a higher probability of developing fever at a subsequent dose of BEXSERO if the subject experienced fever at the preceding dose(s).

More subjects used antipyretics after vaccination with BEXSERO and routine vaccines simultaneously than did those vaccinated with either BEXSERO or routine vaccines alone (Table 2). Even though fever rates were higher in subjects vaccinated with BEXSERO and concomitant vaccines, rates for fever in which a medical visit was sought were low and comparable to recipients of Menjugate with routine vaccines and routine vaccines only (Table 2).
Systemic reaction rates were comparable between the 2, 4, 6-month and 2, 3, 4-month schedules for recipients of BEXSERO with routine vaccines. For those subjects who received BEXSERO alone in the 2, 4, 6-month schedule without concomitant vaccines, fever rates were reduced (26% to 41% across the three doses) and comparable to the rates in subjects receiving only the routine infant vaccines.

Table 1 - Percentage of Infants Experiencing Local Reactions on Days 1-7 Following Vaccination with BEXSERO and Routine Vaccines (Infanrix hexa, Prevnar) at 2, 4, and 6 Months of Age

	Percentage of Subjects With Injection Site Reactions (Severe or >100mm[a])			
	Dose	**BEXSERO Site[b]**	**Infanrix hexa Site[c]**	**Prevnar Site[d]**
	1	**N=3101**	**N=3102**	**N=3102**
	2	**N=3044**	**N=3047**	**N=3047**
	3	**N=3019**	**N=3023**	**N=3022**
Tenderness	1	66(14)	56(11)	54(11)
	2	66(14)	57(11)	55(11)
	3	65(14)	58(12)	56(11)
Erythema	1	60(<1)	46(0)	41(0)
	2	63(0)	57(0)	49(0)
	3	64(<1)	58(0)	52(0)
Induration	1	51(0)	33(0)	25(0)
	2	54(0)	47(0)	35(0)
	3	55(0)	49(0)	36(0)
Swelling	1	26(<1)	16(0)	13(0)
	2	27(<1)	21(0)	17(0)
	3	31(<1)	23(0)	19(0)

[a] Severe tenderness - cried when injected limb was moved; erythema, induration and swelling - >100 mm;
[b] BEXSERO: combined data of BEXSERO (studies V72P12 and V72P13) administered concomitantly with routine vaccines (Infanrix hexa, Prevnar) in a 2, 4, 6-month schedule;
[c] Infanrix hexa vaccine administered in a 2, 4, 6-month schedule (studies V72P12 and V72P13);
[d] Prevnar vaccine administered in a 2, 4, 6-month schedule (studies V72P12 and V72P13).

Table 2 - Percentage of Infants Experiencing Systemic Reactions on Days 1-7 Following Vaccination with BEXSERO and Routine Vaccines (Infanrix hexa, Prevnar) at 2, 4 and 6 Months of Age

	Percentage of Subjects With Systemic (Severe[a])Reactions			
	Dose	**BEXSERO+Routine Vaccines Group[b]**	**Menjugate+Routine Vaccines Group[c]**	**Routine Vaccines Only Group[d]**
	1	**N=3102**	**N=490**	**N=659**
	2	**N=3046-3048**	**N=478-479**	**N=654**
	3	**N=3023-3024**	**N=470-471**	**N=651**
Change Eat. Habits	1	51(3)	31(1)	30(2)
	2	44(3)	32(1)	25(<1)
	3	43(3)	29(1)	25(2)
Sleepiness	1	72(3)	58(4)	56(2)
	2	64(2)	45(1)	42(<1)
	3	53(1)	35(1)	32(<1)
Vomiting	1	13(1)	11(<1)	7(<1)
	2	13(<1)	11(1)	6(<1)
	3	12(<1)	9(<1)	7(<1)
Diarrhea	1	24(1)	20(1)	17(1)
	2	22(1)	15(<1)	17(<1)
	3	18(1)	13(1)	12(<1)
Irritability	1	79(6)	55(3)	61(2)
	2	79(7)	58(4)	62(3)
	3	76(6)	49(3)	54(1)
Unusual Crying	1	69(5)	52(3)	41(2)
	2	66(5)	50(4)	40(2)
	3	56(4)	39(3)	30(2)
Rash (Urticarial)	1	5(1)	4(<1)	3(1)
	2	6(2)	4(<1)	5(1)
	3	5(1)	3(0)	5(1)
		Other Solicited Outcomes		
Fever ≥38°C[e] (≥40°C)	1	75(<1)	46 (0)	44(<1)
	2	79(1)	63(<1)	59(<1)
	3	69(1)	42(0)	50(1)
Analgesic/ Antipyretic Medication use[f]	1	75	40	43
	2	81	52	52
	3	71	36	45
Medically Attended Fever[g]	1	1	1	1
	2	1	1	<1
	3	1	2	1

[a] Definition of severe: change in eating habits-missed >2 feeds; sleepiness-sleeps most of the time, hard to arouse; vomiting-little/no intake for more prolonged time; diarrhea - ≥ 6 liquid stools, no solid consistency; Irritability-unable to console; Unusual crying-unusual, high pitched, screaming, unlike the child's normal crying, that persists for ≥3 hours;

[b] BEXSERO+Routine Vaccines Group: combined data (studies V72P12 and V72P13) from BEXSERO administered concomitantly with routine vaccines (Infanrix hexa, Prevnar) at a 2, 4, 6-month schedule;

[c] Menjugate+Routine Vaccines Group: data from Menjugate administered concomitantly with routine vaccines (Infanrix hexa, Prevnar) from study V72P13 at a 2, 4, 6-month schedule;

[d] Routine Vaccines Only Group: data from routine vaccines (Infanrix hexa, Prevnar) administered at a 2, 4, 6-month schedule from study V72P13;

[e] Fever is based on actual temperature recorded with no adjustment for route of measurement.

Body temperature was measured mainly by the rectal route in study V72P13; in study V72P12 body temperature was measured by both the rectal and axillary routes (30-31% rectal, 58-61% axillary);

[f] Percentage of subjects who were treated with analgesic or antipyretic medication during the day 1-7 time period after study vaccination;

[g] Percentage of subjects who had fever for which a medical visit was sought during the day 1-7 time period after study vaccination.

In an additional study, V72P16, BEXSERO was administered with Infanrix hexa and Prevnar at 2, 3 and 4 months of age, with or without prophylactic acetaminophen. Data from this study showed that there is a statistically significant reduction in the percentage of subjects reporting fever both within 3 days and 7 days after vaccination when prophylactic acetaminophen treatment is adopted, without impacting the immune responses (see Part II, Immunogenicity Data).

Data on local and systemic reactions in children less than 2 years of age receiving either a fourth dose (booster) or two catch-up doses of BEXSERO are shown in Table 3 and Table 4. Additional data for a fourth dose of BEXSERO at 12 months of age in study V72P16 (after three doses at 2, 3 and 4 months of age) and at 12, 18 or 24 months of age in study V72P12E1 (after three doses at either 2, 4 and 6 months of age or 2, 3 and 4 months of age) confirmed these results. Data for a two-dose catch-up schedule of BEXSERO at either 12 and 14 or 18 and 20 months of age in control subjects who received only the routine infant vaccines in V72P12 are also in line with these observations.

In general, the majority of the local and systemic reactions following either a fourth dose or two-dose catch-up series of BEXSERO were transient, and most were mild or moderate in severity. Reactions (except tenderness) did not become more frequent after the second catch-up dose of BEXSERO.

Table 3 - Percentage of Children (less than 2 years of age) Experiencing Local Reactions on Days 1-7 Following Vaccination with a Fourth Dose of BEXSERO at 12 Months of Age or with Two Catch-Up Doses of BEXSERO at 13 and 15 or 12 and 14 Months of Age, With or Without Concomitant Priorix-Tetra

		Percentage of Subjects With Injection Site Reactions (Severe or >50mm[a])			
		4th Dose of BEXSERO		Two Catch-up Doses of BEXSERO	
	Schedule	BEXSERO with Priorix-Tetra at 12 mos.	BEXSERO at 12mos.	Dose 1: Priorix-Tetra at 12 mos. Dose 2: BEXSERO at 13 mos. Dose 3: BEXSERO at 15 mos.	Dose 1: BEXSERO with Priorix-Tetra at 12 mos. Dose 2: BEXSERO at 14 mos.
		N=765	N=789	N=281	N=117
	Dose				
Tenderness	1	71(14)	71(15)	20(1)[b]	57(10)
	2	-	-	56(10)	67(18)
	3	-	-	66(16)	-
Erythema	1	66(8)	68(7)	42(0)[b]	68(2)
	2	-	-	62(1)	60(2)
	3	-	-	58(3)	-
Induration	1	51(4)	54(3)	19(0)[b]	49(1)
	2	-	-	40(<1)	46%(<1)
	3	-	-	42 (<1)	-
Swelling	1	37(6)	36(5)	9(0)[b]	31(1)
	2	-	-	29(1)	28(1)
	3	-	-	30(3)	-

[a] Severe tenderness-cried when injected limb was moved; erythema, induration and swelling - >50 mm;
[b] Local reactions at the Priorix-Tetra injection site;
mos: months.

Table 4 - Percentage of Children (less than 2 years of age) Experiencing Systemic Reactions on Days 1-7 Following Vaccination with a Fourth Dose of BEXSERO at 12 Months of Age or with Two Catch-Up Doses of BEXSERO at 13 and 15 or 12 and 14 Months of Age, With or Without Concomitant Priorix-Tetra

		Percentage of Subjects With Systemic Reactions (Severe[a])			
		4th Dose of BEXSERO		Two Catch-up Doses of BEXSERO	
	Schedule	BEXSERO with Priorix-Tetra at 12 mos.	BEXSERO at 12 mos.	Dose 1: Priorix-Tetra at 12 mos. Dose 2: BEXSERO at 13 mos. Dose 3: BEXSERO at 15 mos.	Dose 1: BEXSERO with Priorix-Tetra at 12 mos. Dose 2: BEXSERO at 14 mos.
		N=764-765	N=789	N=274-284	N=116-117
	Dose				
Change in Eating Habits	1	41(2)	40(2)	25(1)	38(0)
	2	-	-	34(1)	37(3)
	3	-	-	30(2)	-
Sleepiness	1	47(1)	45(1)	30(<1)	47(1)
	2	-	-	39(1)	41(0)
	3	-	-	39(1)	-
Vomiting	1	7(<1)	5(<1)	7(0)	2(0)
	2	-	-	5(<1)	3(1)
	3	-	-	3(0)	-
Diarrhea	1	25(1)	20(1)	16(1)	29(0)
	2	-	-	15(0)	22(0)
	3	-	-	15(0)	-
Irritability	1	73(4)	68(3)	43(1)	70(3)
	2	-	-	60(2)	63(3)
	3	-	-	56(3)	-
Unusual Crying	1	43(2)	37(2)	19(1)	35(2)
	2	-	-	28(1)	36(3)
	3	-	-	27(1)	
Rash (Urticarial)	1	7(3)	7(2)	7(3)	8(1)
	2	-	-	5(2)	3(2)
	3	-	-	4(1)	
Fever ≥38°C (≥40°C)	1	47(1)	41(<1)	24(<1)	46(0)
	2	-	-	37(0)	43(0)
	3	-	-	35 (<1)	-
Antipyretic Medication use[b]	1	57	51	23	57
	2	-	-	42	50
	3	-	-	39	-
Med. Attended Fever[c]	1	1	2	1	1

	Percentage of Subjects With Systemic Reactions (Severe[a])			
	4th Dose of BEXSERO		Two Catch-up Doses of BEXSERO	
Schedule	BEXSERO with Priorix-Tetra at 12 mos.	BEXSERO at 12 mos.	Dose 1: Priorix-Tetra at 12 mos. Dose 2: BEXSERO at 13 mos. Dose 3: BEXSERO at 15 mos.	Dose 1: BEXSERO with Priorix-Tetra at 12 mos. Dose 2: BEXSERO at 14 mos.
	N=764-765	N=789	N=274-284	N=116-117
2	-	-	0	2
3	-	-	1	-

[a] Definition of severe: change in eating habits-missed >2 feeds; sleepiness-sleeps most of the time, hard to arouse; vomiting-little/no intake for more prolonged time; diarrhea - ≥ 6 liquid stools, no solid consistency; Irritability-unable to console; Unusual crying-unusual, high pitched, screaming, unlike the child's normal crying, that persists for ≥3 hours;

[b] Percentage of subjects who were treated with any antipyretic medication during the day 1-7 time period after study vaccination;

[c] Percentage of subjects who had fever for which a medical visit was sought during the day 1-7 time period after study vaccination;

mos: months

Children (aged 2 years through 10 years)

The characterization of the safety profile of BEXSERO in this population is based on data from 4 studies in more than 290 subjects: V72P12E1 and V72P13E2 in children 24 months of age, V72P6E1 and V72P9E1 in children 40 to 60 months of age. In all these studies, the schedule investigated was a two-dose primary series of BEXSERO administered with an interval of 2 months between doses.

Data on local and systemic reactions following vaccination with BEXSERO in children 2 through 10 years of age are shown in Table 5 and Table 6. Most of the solicited reactions were mild or moderate in severity and transient. The percentages of subjects with fever ranged from 10% to 28% in this age group. These rates were lower with increasing age. Few children (0-3% of subjects) experienced body temperature ≥ 40°C. Fever associated with BEXSERO vaccination occurred early after vaccination, and was transient, with the majority resolving within 2 days. Medically attended fever events occurred in no more than 3% of children.

Table 5 - Percentage of Children (2 to 10 Years of Age) Experiencing Local Reactions on Days 1-7 Following Vaccination with BEXSERO

	Percentages of Subjects With Any (Severe) Reaction				
Age	**24 to 26 months**		**40-44 months**		**60-62 months**
Study	**V72P12E1**	**V72P13E2**	**V72P6E1**	**V72P9E1**	**V72P9E1**
Local	**(N=54)**	**(N=112)**	**(N=42)**	**(N=41)**	**(N=48)**

Reaction	Dose					
Pain	1	-	-	93 (21)	87 (8)	92 (10)
	2*	-	-	85 (15)	95 (24)	91 (13)
Tenderness	1	87 (26)	88 (10)	-	-	-
	2*	81 (35)	89 (18)	-	-	-
Erythema	1	72 (2)	77 (0)	98 (0)	92 (0)	94 (0)
	2*	60 (0)	73 (1)	93 (0)	97 (0)	87 (0)
Induration	1	50 (0)	49 (0)	33 (0)	44 (0)	40 (0)
	2*	42 (0)	56 (0)	49 (0)	49 (0)	44 (0)
Swelling	1	35 (0)	31 (0)	48 (0)	26 (0)	46 (0)
	2*	37(0)	39 (0)	63 (0)	41 (0)	44 (0)

* local reaction after second dose was evaluated in at least N=52 in study V72P12E1, N=108 in study V72P13E2, N=41 in study V72P6E1, N=37 in study V72P9E1 (40-44 months cohort) and N=45 in study V72P9E1 (60-62 months cohort).

Table 6 - Percentage of Children (2 to 10 Years of Age) Experiencing Systemic Reactions Days 1-7 Following Vaccination with BEXSERO

		Percentages of Subjects With Any (Severe) Reaction				
	Age	24 to 26 months		40-44 months		60-62 months
Systemic Reaction	Study / Dose	V72P12E1 (N=54)	V72P13E2 (N=112)	V72P6E1 (N=42)	V72P9E1 (N=39)	V72P9E1 (N=48)
Change Eat. Habits	1	46 (2)	34 (0)	38 (2)	33 (3)	21 (2)
	2*	40 (4)	36 (3)	34 (0)	35 (3)	22 (2)
Sleepiness	1	33 (2)	46 (0)	48 (5)	51 (8)	40 (6)
	2*	35 (0)	46 (3)	37 (2)	46 (8)	30 (0)
Vomiting	1	11 (2)	8 (0)	2 (0)	3 (0)	10 (0)
	2*	8 (2)	5 (0)	0	11 (0)	7 (0)
Diarrhea	1	37 (0)	13 (0)	14 (0)	5 (0)	4 (0)
	2*	13 (4)	12 (0)	2 (0)	5 (0)	4 (0)
Irritability	1	52 (7)	59 (2)	76 (7)	62 (0)	44 (4)
	2*	44 (4)	58 (5)	59 (5)	62 (5)	43 (2)
Unusual Crying	1	28 (2)	33 (1)	-	-	-
	2*	29 (4)	27 (3)	-	-	-
Headache	1	-	-	10 (0)	10 (0)	13 (2)
	2*	-	-	10 (2)	11 (0)	20 (0)
Arthralgia	1	-	-	31 (7)	23 (3)	31 (2)
	2*	-	-	22 (7)	19 (5)	33(2)
Rash	1	4 (0)	7 (3)	2 (2)	5 (0)	6 (0)
	2*	0	6 (0)	5 (0)	3 (0)	9 (2)
Fever [Body	1	28 (0)	21 (0)	10 (0)	15 (3)	10 (0)

		Percentages of Subjects With Any (Severe) Reaction				
	Age	**24 to 26 months**		**40-44 months**		**60-62 months**
Systemic Reaction	**Study Dose**	**V72P12E1 (N=54)**	**V72P13E2 (N=112)**	**V72P6E1 (N=42)**	**V72P9E1 (N=39)**	**V72P9E1 (N=48)**
Temp. ≥38°C (≥40°C)]	2*	25 (0)	26 (1)	12 (0)	11 (0)	11 (0)
Medical Attended Fever	1	2 (-)	0 (-)	0 (-)	0 (-)	0 (-)
	2*	0 (-)	2 (-)	0 (-)	3 (-)	0 (-)

* systemic reaction after second dose was evaluated in at least N=52 in study V72P12E1, N=108 in study V72P13E2, N=41 in study V72P6E1, N=37 in study V72P9E1 (40-44 months cohort) and N=46 in study V72P9E1 (60-62 months cohort)

Adolescents (aged 11 years through 17 years)

The characterization of the safety profile of BEXSERO in the adolescent population aged 11 through 17 years was based on data from study V72P10.
One, two or three doses of BEXSERO were administered to adolescents according to one of the following schedules: 0, 0-1, 0-2 or 0-1-2 months.
The data supporting the safety and tolerability of the two-dose vaccination schedules for adolescents were generated from the first and second doses of the schedules investigated in this study.
Data on local and systemic reactions are shown in Table 7.

Reports of fever following BEXSERO vaccination were infrequent (3-4% across vaccinations) and were comparable to the rates observed in adolescents receiving placebo (2-4%).

The frequency of reports for local and systemic reactions did not increase with the second dose of BEXSERO, and the majority of the reactions were transient.

Additional safety data on BEXSERO in adolescents relative to the administration of one dose at month 6 from study V72P10 and for 2 doses 1 month apart in study V72_41 were in line with these observations.

Table 7 - Percentage of Adolescents (aged 11-17 Years) Experiencing Local and Systemic Reactions on Days 1-7 Following Vaccination with BEXSERO

	Percentage of Subjects With Any (Severe[a]) Reaction		
	Study Schedule	**V72P10 (Combined Month 0, 0-1, 0-2)**	
	Age	**11-17 years**	
	Dose	**BEXSERO**	**Placebo[b]**
	1	**N=1503**	**N=128**
	2	**N=1039**	**N=124**
Local Reactions			
Erythema	1	54(<1)	40(0)
	2	51(<1)	31(0)
Induration	1	40(<1)	27(0)
	2	40(<1)	23(0)
Swelling	1	39(<1)	20(0)
	2	38(1)	15(0)
Pain	1	91(17)	86(9)
	2	85(15)	71(9)
Systemic Reactions			
Malaise	1	56(7)	48(3)
	2	50(7)	35(2)
Myalgia	1	45(7)	41(4)
	2	40(6)	40(3)
Arthralgia	1	24(2)	19(0)
	2	21(3)	16(1)
Headache	1	46(5)	37(2)
	2	42(5)	33(3)
Nausea	1	19(1)	17(2)
	2	16(2)	15(1)
Fever ≥38°C (≥40°C)	1	3(0)	4(0)
	2	4(0)	2(0)
Other Solicited Outcomes			
Analgesic/antipyretic use[c]	1	35	20
	2	27	15
Stayed home due to reaction[d]	1	16	6
	2	11	3

[a] Severe erythema, induration and swelling - >100 mm; severe pain and systemic reactions - unable to perform normal daily activity;
[b] Placebo administered in month 0-1 schedule;
[c] Percentage of subjects who were treated with analgesic or antipyretic medication during the day 1-7 time period after study vaccination;
[d] Collected as yes or no

Adults (aged 18 years through 50 years)

Limited safety data were collected in studies V72P5 (N=28) and V72P4 (N=53) in adults 18 to 40 and 18 to 50 years of age, respectively. The most commonly reported local reaction was pain, ranging from 82% to 98% across studies and two vaccine doses. The most commonly reported systemic reactions were malaise, myalgia and headache, ranging from 14% (malaise) to 57% (myalgia) across studies and two vaccine doses. Reports of fever following BEXSERO vaccination were infrequent (2-4%).

Unsolicited Adverse Events

Regardless of the age and of the vaccination schedule, there was no major difference in the percentages of subjects reporting unsolicited AEs (Adverse Events) within 1 month of the last vaccination or during the safety follow-up period between the BEXSERO given alone or in combination with routine vaccinations and comparator groups. Only a few AEs were assessed as possibly or probably related in the safety follow up period.

Infants and Children (less than 2 years of age)

Between study day 1 and 7 months of age (1 month after the third dose), the percent of subjects experiencing unsolicited AEs in the BEXSERO with concomitant routine vaccines, Menjugate with concomitant routine vaccines, and routine vaccines only groups are shown in Table 8. Overall, between study day 1 and 7 months of age, the most commonly reported AEs after any vaccination with BEXSERO were injection site reactions (most considered as possibly related to vaccination as these local reactions of induration, erythema, and swelling were solicited AEs continuing after the 7-day vaccination window) and upper respiratory tract infections (10%; mostly considered unrelated to vaccination).

Table 8 - Overview of Unsolicited Adverse Events of BEXSERO Administered with Concomitant Routine Vaccines at 2, 4 and 6 Months of Age, Collected From Study Day 1 to 7 Months of Age, by Vaccine Group

	Percentage of Subjects with Adverse Events		
	BEXSERO+Routine Vaccines Group[a] N=3155	**Menjugate+Routine Vaccines Group[b] N=488**	**Routine Vaccines Only Group[c] N=658**
Any AEs	77	63	71
At least possibly related AEs	52	42	34
Serious AEs	4	3	3

[a] BEXSERO+Routine Vaccines Group: combined data (studies V72P6, V72P12 and V72P13) from BEXSERO administered concomitantly with routine vaccines (Infanrix hexa, Prevnar) at a 2, 4, 6-month schedule;
[b] Menjugate+Routine Vaccines Group: data from Menjugate administered concomitantly with routine vaccines (Infanrix hexa, Prevnar) at a 2, 4, 6-month schedule from study V72P13;
[c] Routine Vaccines Only Group: data from routine vaccines (Infanrix hexa, Prevnar) administered at a 2, 4, 6-month

schedule from study V72P13;
AEs: Adverse Events.

The percentage of subjects who experienced unsolicited AEs after a two-dose catch-up schedule of BEXSERO in vaccine naive children (in their second year of life) was 17% after the first dose and 15% after the second dose of the vaccine; 3% had AEs considered by the investigator to be at least possibly related to vaccination and <1% to 6% were considered serious. The most commonly reported AEs were local injection site reactions and systemic reactions that were originally solicited, but continued past day 7 after vaccination. All of the injection site reactions were at least possibly related to study vaccination. The percentage of subjects who experienced unsolicited AEs after the fourth dose of BEXSERO in the second year of life was 44% and 74% for subjects who received BEXSERO alone and those who received BEXSERO with concomitant Priorix-Tetra vaccine, respectively. The most commonly reported AE was injection site induration. Most of the other AEs were due to local injection site reactions and systemic reactions that were originally solicited, but continued past day 7 after the vaccination.

Children (aged 2 years through 10 years)

Data on unsolicited AEs in children 2-10 years of age are shown in Table 9.

Table 9 - Overview of Unsolicited Adverse Events in Children (2 to 10 Years of Age) After the Two-Dose Schedule of BEXSERO

	Percentage of Subjects with Adverse Events				
Age of subjects	**24 to 26 months**		**40-44 months**		**60-62 months**
Study	**V72P12E1**	**V72P13E2**	**V72P6E1**	**V72P9E1**	**V72P9E1**
	N=55	**N=112**	**N=42**	**N=41**	**N=48**
Any AEs	75	86	43	61	38
Possibly related	29	36	14	15	27
SAEs	2	5	2	10	2

Adolescents and Adults

Table 10 provides an overview of unsolicited AEs collected up to study Month 3 in adolescents and adults who received BEXSERO in either the 0-1 month or 0-2 month schedule.
SAEs (Serious Adverse Events) were not reported by any adult subjects. SAEs were infrequently reported (1%) in adolescents.

For both adolescents and adults, the most commonly reported possibly or probably related unsolicited AEs were local injection site reactions (pain, induration, swelling) that continued past the day 7 observation period.

Table 10 - Overview of Unsolicited Adverse Events Collected up to Month 3 in Adolescents and Adults (11 Years of Age and Older), after the Two-Dose Schedule of BEXSERO

	Percentage of Subjects with Adverse Events			
	0-1 Month Schedule[a]		0-2 Month Schedule[b]	
	11 to 17 yoa N=748	18 to 40 yoa N=28	11 to 17 yoa N=380	18 to 50 yoa N=53
Any AEs	43	18	46	32
Possibly or probably related AEs	17	4	16	13
Serious AEs	1	0	1	0

[a] 0-1 schedule: BEXSERO was administered at months 0 and 1 in the 18 to 40 years of age (study V72P5) and at months 0 and 1 in the 11 to 17 years of age (study V72P10);
[b] 0-2 schedule: BEXSERO was administered at months 0 and 2 in the 18 to 50 years of age (study V72P4) and at months 0 and 2 in the 11 to 17 years of age (study V72P10);
yoa: years of age;
vs: versus;
AEs: Adverse Events.

Less Common Drug Reactions Seen in Clinical Trials (<1%)

Adverse reactions (following primary immunization or additional dose) considered as being at least possibly related to vaccination have been categorized by frequency.

Frequencies are defined as follows:
Uncommon: ≥ 1/1,000 to < 1/100
Rare: ≥ 1/10,000 to < 1/1,000

Infants and Children (less than 2 years of age)

General disorders and administration site conditions
Uncommon: fever (≥40°C)

Nervous system disorders
Uncommon: seizures (including febrile seizures)

Skin and subcutaneous tissue disorders
Uncommon: eczema, urticaria

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

Post-Market Adverse Drug Reactions

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

General disorders and administration site conditions
Blisters at or around the injection site

Immune system disorders
Allergic reactions (including anaphylactic reactions)

Nervous system disorders
Syncope or vasovagal responses to injection

DRUG INTERACTIONS

Drug-Drug Interactions

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 and varicella (see Part II, CLINICAL TRIALS, Immunogenicity Data, *Concomitant use of BEXSERO with routine vaccines*).

As higher percentages of subjects reported systemic reactions, including fever, change in eating habits, tenderness at the injection site and irritability, following BEXSERO given concomitantly with routine vaccines than after BEXSERO alone, separate vaccinations can be considered when possible. In addition, fever was mostly reported during the 1-4 days after vaccination with Bexsero alone and during the 5-28 days after the MMRV vaccination alone.
Prophylactic use of acetaminophen reduces the incidence and severity of fever without affecting the immunogenicity of either BEXSERO or most antigens of routine vaccines. The effect of antipyretics other than acetaminophen on the immune response has not been studied.

Concomitant administration of BEXSERO with vaccines other than those mentioned above has not been studied.

When given concomitantly with other vaccines, BEXSERO should be administered at different injection site.

Drug-Lifestyle Interactions

BEXSERO has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section ADVERSE REACTIONS may temporarily affect the ability to drive or use machines.

DOSAGE AND ADMINISTRATION

Dose of 0.5 mL.

Recommended Dose and Dosage Adjustment

Infants aged 2 months through 5 months

The recommended immunisation series consists of four doses, each of 0.5 mL. The primary infant series consists of three doses, given at 2, 4 and 6 months of age, followed by a fourth dose (booster).

The primary series can also be given at 2, 3 and 4 months of age, but the immune response to the NHBA antigen is lower (see Table 13).

With both schedules, a fourth dose (booster) is required in the second year of life between 12 and 23 months of age. It is preferred this dose be given early in the second year of life, whenever possible.

Unvaccinated infants aged 6 months through 11 months

The vaccination schedule consists of three doses each of 0.5 mL with an interval of at least 2 months between the first and second dose. A third dose is required in the second year of life with an interval of at least 2 months between the second and third dose. The need for further booster doses has not been established.

Unvaccinated children aged 12 months through 23 months

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

Children aged 2 years through 10 years

The vaccination schedule consists of two doses, each of 0.5 mL, with an interval of at least 2 months between doses. The need for a subsequent dose after this immunisation schedule has not been established.

Individuals aged 11 years through 17 years

The vaccination schedule consists of two doses, each of 0.5 mL, with an interval of at least 1 month between doses. The need for a subsequent dose after this vaccination schedule has not been established.

Administration

BEXSERO should be given by deep intramuscular injection, preferably in the anterolateral aspect of the thigh in infants or in the deltoid muscle region of the upper arm in older subjects.

Separate injection sites must be used if more than one vaccine is administered at the same time. The vaccine must not be injected intravenously, subcutaneously or intradermally and must not be mixed with other vaccines in the same syringe.

BEXSERO must not be mixed with other medicinal products.

OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional Poison Control Centre

ACTION AND CLINICAL PHARMACOLOGY

Epidemiology Data

IMD is an important cause of meningitis and septicemia, which can lead to mortality (9% in Canada), increasing with age, or permanent sequelae (11-19%) despite appropriate antimicrobial therapy. Pharyngeal carriage rates of meningococci are highest in adolescents (20-30%).

There are 13 diverse polysaccharide capsules but only A, B, C, W-135, and Y serogroups commonly cause IMD. Since the decline in serogroup C disease after the implementation of meningococcal conjugate C immunisation programs, serogroup B has become the leading cause of IMD in Canada. According to the 2013 Canadian Communicable Disease Report (1), serogroup B is increasing in distribution (57% of all serogroups) and incidence (0.4 per 100,000). The highest incidence of serogroup B occurs in infants under 1 year of age (80% of cases or 5.5per 100,000 in 2007, up to 6.16 per 100,000 in 2009), followed by children from 1 to 4 years of age (67% of cases or 1.28per 100,000 in 2007, up to 1.35 in 2008) (1, 2). The incidence in young children is higher than that of serogroup C before the implementation of serogroup C immunisation programs. Other peaks occur in 15 to 19 years (62% of cases or 0.8 per 100,000) and 20 to 24 years of age (71% of cases or 0.66 per 100,000). Since 2003, Québec

has seen the introduction and increase of a strain of serogroup B *N. meningitidis* identified as B:17:P1.19 sequence type ST-269 with 43 out of 198 (22%) serogroup B cases reported in Québec between 2002 and 2011 (2). From 2009 to 2011 in Québec, serogroup B has been responsible for 88% of all IMD cases reported to laboratory surveillance and 61% of all IMD deaths where 65% of serogroup B IMD are caused by this ST-269cc in 2011. During this period, serogroup B was responsible for 100% of laboratory confirmed IMD in infants <1 years of age, 94% in 1-24 year olds, 76% in 25-64 year olds and 58% in those ≥ 65 years of age (3).

The potential of BEXSERO to protect against diverse invasive serogroup B strains isolated in Canada was studied using the Meningococcal Antigen Typing System (MATS) that was specifically developed to estimate coverage by the primary antigens present in BEXSERO. The MATS was established 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). As the antigens, including NHBA, NadA, fHbp, and PorA P1.4, are variably expressed by different strains, meningococci that express them at sufficient levels are susceptible to killing by vaccine-elicited antibodies (4).

A survey of approximately 157 invasive serogroup B isolates collected during 2006-2009 by the IMPACT surveillance network (Immunization Monitoring Program ACTive) revealed that 66% of isolates had an appropriate type and sufficient antigen content and were predicted to be covered by BEXSERO, with empirical variability in coverage from 43% to 78%. The survey utilized the bactericidal thresholds that were derived using serum pools from 13-month old infants after 4 immunizations of BEXSERO at 2, 4, 6 and 12 months of age. Coverage for the Canadian hyper-endemic strains, the two most prevalent strains (sequence type ST-269 and ST-154) was 95% and 100%, with empirical variability in coverage ranging from 43% to 97% and 100% to 100%, respectively (5). As MATS coverage predictions are based on killing of meningococci by immune serum pools and not individual subject sera, this prediction is subject to certain limitations and its accuracy may only be verified upon vaccine use. The vaccine appears to provide coverage across a wide diversity of endemic strains and is not limited to protecting against one or two subtypes. At least 40% of isolates were covered by two or more vaccine antigens, with fHbp and NHBA contributing the most to vaccine coverage (5).

For epidemiology and further information specific to Canada, please consult Canada Communicable Disease Reports ACS-3 (April 2009) (6), ACS-4 (June 2009) (7) and ACS-1 (January 2013) (1), http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/13vol39/acs-dcc-1/index-eng.php.

Mechanism of Action

BEXSERO is a vaccine containing both purified, recombinant protein antigens and OMV derived from *N. meningitidis*. Protection against IMD is mediated mainly by bactericidal antibodies directed against components of the bacterium. Immunization with BEXSERO is intended to raise the titer of bactericidal antibodies that specifically bind the vaccine antigens

fHbp, NadA, NHBA and PorA P1.4 (the immunodominant antigen present in the OMV component). Meningococci that express either the PorA P1.4 antigen or sufficient levels of any of the other antigens (NadA, fHbp, NHBA), defined as the positive bactericidal threshold, are predicted to be susceptible to killing by vaccine-elicited immune serum (see **ACTION AND CLINICAL PHARMACOLOGY, Epidemiology Data)**.

Pharmacodynamics

Clinical Efficacy

No clinical efficacy studies have been undertaken with BEXSERO.
The efficacy of BEXSERO has been inferred by measuring bactericidal antibody responses to each of the vaccine antigens fHbp, NadA, NHBA and PorA P1.4, using a set of four meningococcal serogroup B reference strains (H44/76, 5/99, M10713 and NZ98/254, respectively). However, data are not available from all vaccine schedules using strain M10713. Two reference strains (strains H44/76 and 5/99) were selected for hSBA with high level expression of the antigens included in the vaccine, as compared to most of the circulating strains. These two strains could generate a higher percentage of subjects with hSBA ≥1:5 and higher GMTs than the strains with a low expression (if selected as the reference strains). Although the reference strains are intended to evaluate how well vaccinees mount a functional, antigen-specific immune response against the vaccine antigens, using the strains with high level of antigen expression could potentially result in a more favourable outcome than strains with low level of expression.
Bactericidal antibodies against these strains were measured by hSBA.

The studies of Goldschneider et al. demonstrated an inverse relationship between meningococcal disease incidence and prevalence of hSBA for serogroups B, C, and A (8, 9). The experience with outer membrane vesicle (OMV) vaccines supports this observation where the percentage of subjects with SBA ≥4 was similar to the estimated efficacy rates (10). It is generally recognised that the surrogate of protection for serogroup B meningococci is the hSBA even though the immune responses are not directed against capsular polysaccharide antigens (11, 12).

Immunogenicity was evaluated in randomized, multicenter, clinical trials that enrolled infants, children (less than 2 years of age), adolescents and adults (see Part II, CLINICAL TRIALS).

Pharmacokinetics

Evaluation of pharmacokinetic properties is not required for vaccines; therefore, no pharmacokinetic studies have been conducted with the vaccine.

Duration of Effect

The duration of post vaccination immune status has not been established.

STORAGE AND STABILITY

Store in a refrigerator at 2°C to 8°C.
Do not freeze. Do not use vaccine that may have been frozen.
Protect the vaccine from light.

The expiry date of the vaccine is indicated on the label and packaging.
Do not use the vaccine after the expiry date shown on the label.

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

SPECIAL HANDLING INSTRUCTIONS

A fine off-white deposit may form when the product stands for a long period.
Shake the vaccine well before use to form a homogeneous suspension. The vaccine should be visually inspected for particulate matter and discoloration prior to administration.

In the event of any foreign particulate matter and/or variation of physical aspect being observed, do not administer the vaccine.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

BEXSERO is a white opalescent liquid suspension for intramuscular injection.

Composition

1 dose (0.5 mL) contains:

Recombinant *Neisseria meningitidis* serogroup B NHBA fusion protein[1, 2, 3]	50 micrograms
Recombinant *Neisseria meningitidis* serogroup B NadA protein[1, 2, 3]	50 micrograms
Recombinant *Neisseria meningitidis* serogroup B fHbp fusion protein[1, 2, 3]	50 micrograms
Outer membrane vesicles (OMV) from *Neisseria meningitidis* serogroup B strain NZ98/254 measured as amount of total protein containing the PorA P1.4[2]	25 micrograms

[1] Produced in *E. coli* by recombinant DNA technology.
[2]Adsorbed on aluminum hydroxide (0.5 mg Al^{+3}).
[3]NHBA (Neisseria Heparin Binding Antigen), NadA (Neisserial adhesin A), fHbp (factor H

binding protein).

Additional excipients
Sodium chloride, histidine, sucrose, water for injections.

Packaging

BEXSERO is supplied as a 0.5 mL suspension in a pre-filled syringe (Type I glass).

The tip cap of the syringe may contain natural rubber latex (see section WARNINGS AND PRECAUTIONS).

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Multicomponent Meningococcal B Vaccine (recombinant, adsorbed)

Product Characteristics

BEXSERO is a multicomponent Meningococcal B Vaccine and appears as white opalescent liquid suspension for intramuscular injection in a prefilled syringe (see Part I, DESCRIPTION).

CLINICAL TRIALS

Study Demographics and Trial Design

The safety and immunogenicity profile of BEXSERO is based on data from 15 clinical studies (see Table 11).

Table 11 - Study Demographics and Trial Designs

Study No.	Age at Enrollment	Trial design	Dosage, route of administration and schedule	No. of subjects enrolled (No. receiving BEXSERO[a])	Mean age of enrolled subjects (range)	Gender of enrolled subjects (% male)
V72P4 Phase 2	18-50 yrs	Open-label, multicenter Safety, immunogenicity in at-risk adults	0.5mL, IM Schedule: 0, 2, 6 mos	54 (53)	31.8 (21-46) yrs	50%
V72P5 Phase 1	18-40 yrs	Observer-blind single center, randomized Safety, immunogenicity in healthy adults	0.5mL, IM Schedule: 0, 1, 2 mos	70 (28)	32.1 (18-40) yrs	66%
V72P6 Phase 2	2 mos	Open-label, multicenter, randomized, controlled Safety, immunogenicity of infant primary series + fourth dose	0.5mL, IM Schedule: 2, 4, 6 12 mos of age	147 (74) (50: 4-doses; 24: one dose at 12 mos of age)	60.2 (55-85) days	58%
V72P6E1 Phase 2	40-60 mos	Open-Label, single center, extension Antibody persistence, safety and immunogenicity of booster doses in children who received 1 or 4 doses as infants in study V72P6	0.5mL, IM Schedule: 5th dose boost at 40 mos; 2 doses at 40, 42 mos after one dose at 12 mos; 2 catch up doses in naive children at 40, 42 mos.	113 (69) (19: 5th dose; 8: 2-doses after one dose at 12 mos; 42: 2-doses in naïve)	41.5 (40-44) mos	50%
V72P9 Phase 2	6-8 mos	Single-blind, single center, randomized Safety, immunogenicity of infant primary series + third dose	0.5mL, IM Schedule: 6, 8 12 mos of age	60 (30)	7.1 (6-8) mos	47%

Study No.	Age at Enrollment	Trial design	Dosage, route of administration and schedule	No. of subjects enrolled (No. receiving BEXSERO[a])	Mean age of enrolled subjects (range)	Gender of enrolled subjects (% male)
V72P9E1 Phase 2	40-60 mos	Open-label, single center, extension Antibody persistence, safety, and immunogenicity of booster dose in children who received a 3-dose series as infants in Study V72P9	0.5mL, IM Schedule: 4th dose boost at 40 mos; 2 catch up doses in naive children at 40,42 or 60,62 mos	120 (103) (14: 4th dose; 89: 2-doses in naïve)	50.0 (39-62) mos	48%
V72P10 Phase 2b/3	11-17 yrs	Observer-blind, multicenter, randomized, placebo controlled Safety, immunogenicity, schedule finding	0.5mL, IM Schedule: mos 0; mos 6; mos 0, 1; mos 0, 2; mos 0, 6; mos 0, 1, 2; mos 0, 1, 6; mos 0, 2, 6	1631 (1622)	13.8 (10-17) yrs	44%
V72P10E1 Phase 2b/3	13-19 yrs	Multi-Center, Extension Antibody Persistence	n.a[b]	817 (n.a)	15.9 (13-20) yrs	43%
V72P12 Phase 2b	2 mos	Open-label, multicenter, randomized, controlled Safety, immunogenicity, schedule finding	0.5mL, IM Schedule: 2, 4, 6 and 2, 3, 4 mos of age	1885 (1570)	68.7 (50-107) days	51%
V72P12E1 Phase 2b	12, 18, 24 mos	Open-label, multicenter, extension Safety, immunogenicity of booster in subjects who received a 3-dose series as infants in Study V72P12	0.5mL, IM Schedule: 4th dose booster at 12, 18, or 24 mos of age; 2 catch up doses at 12, 14 or 18, 20 or 24, 26 mos of age	1588 (1519) (1174: 4th dose; 345: 2-doses in naïve)	17.1 (11-26) mos	52%
V72P13 Phase 3	2 mos	Partially blinded, multicenter, randomized controlled Safety, immunogenicity, lot	0.5mL, IM Schedule: 2, 4, 6 mos of age	3630 (2480)	73.5 (54-132) days	51%

Study No.	Age at Enrollment	Trial design	Dosage, route of administration and schedule	No. of subjects enrolled (No. receiving BEXSERO[a])	Mean age of enrolled subjects (range)	Gender of enrolled subjects (% male)
		consistency				
V72P13E1 Phase 3	12 mos	Open-label, multicenter, randomized Safety, immunogenicity of fourth dose, 2 catch-up doses starting at 12 or 13 mo for original control group in V72P13	0.5mL, IM Schedule: 4th dose at 12 mos; 1 or 2 catch-up doses starting at 12 or 13, mos of age	2249 (2247) (1555: 4th dose; 692: 1 or 2 catch-up doses)	12.3 (11-15) mos	51%
V72P13E2 Phase 3	24-27 mos	Open label, randomized, multi-center, extension study	0.5mL, IM Schedule: 3rd dose boost at 12 mos after 2 catch up doses at 13 and 15 mos or 12 and 14 mos; 2 catch up doses in naive children (less than 2 years of age) at 24, 26 mos of age	508 (193) (85: 3rd dose; 108: 2-doses in naïve)	25.4 (23-30) mos	52%
V72P16 Phase 2	2 mos	Partially observer-blind, randomized, controlled, multicenter dose-ranging and formulation-finding Safety and immunogenicity	0.5mL, IM Schedule: 2, 3, 4, 12 mos of age	1507 (736)	74.6 (54-91) days	54%
V72_41 Phase 3	11-17 yrs	Observer-blind, multicenter, randomized Safety and immunogenicity, lot consistency	0.5mL, IM Schedule: 0, 1 mos	344 (342)	13.7 (11-17) yrs	55%

[a] Number of subjects in the BEXSERO safety population. Defined as those subjects who were vaccinated with BEXSERO and who provided some post-baseline safety data;

[b] No investigational vaccine was administered in the V72P10E1 study. Only blood samples were obtained for meningococcal serology from all the subjects

IM: intramuscular;

mos: months;

yrs: years.

Table 12 - Study Results

Study	Primary Immunogenicity Objectives	Prospectively Defined Criterion	Outcome
V72P12 **Phase 2b**	• Demonstration of a sufficient immune response to BEXSERO when given concomitantly with routine vaccines to healthy infants at either 2, 4 and 6 or 2, 3 and 4 months of age, by evaluation of hSBA at 1 month after the third vaccination.	• The immune response was considered sufficient if the lower limit of the two-sided 95% CI for the percentage of subjects with hSBA ≥1:5 at 1 month following the third vaccination was ≥70% for all 3 reference strains H44/76, NZ98/254 and 5/99.	Objective was met. • The lower limits of the two-sided 95% CI for the percentage of subjects with hSBA ≥1:5 for the 2, 4, 6-month schedule were: 98% for strain H44/76, 98% for stain 5/99 and 75% for strain NZ98/254. • The lower limits of the two-sided 95% CI for the percentage of subjects with hSBA ≥1:5 for the 2,3,4-month schedule were: 97% for strain H44/76, 99% for strain 5/99 and 76% for strain NZ98/254.
V72P13 **Phase 3**	Two Co-primary Objectives: • To show the consistency of the immune response from 3 lots of BEXSERO, by hSBA GMTs, when administered to healthy infants at 2, 4 and 6 months of age, at 1 month after the third vaccination. • Demonstration of a sufficient immune response to BEXSERO (3 lots combined) when given concomitantly with routine vaccines to healthy infants at 2, 4 and 6 months of age, by evaluation of hSBA at 1 month after the third vaccination.	• The 3 BEXSERO vaccine lots were considered equivalent if for each of the reference strains H44/76, NZ98/254 and 5/99 and each pair of vaccine lots, the two-sided 95% CI of the ratio of GMTs at 1 month after the third vaccination was contained within the interval [0.50, 2.00]. • The immune response was considered sufficient immune if the lower limit of the two-sided 95% CI for the percentage of subjects with hSBA ≥ 1:5 at 1 month following the third vaccination was ≥ 70% for all 3 reference strains H44/76, NZ98/254 and 5/99, for the 3 BEXSERO lots combined.	Objectives were met. • For each reference strain, for all 3 pairs of BEXSERO vaccine lots simultaneously, the two-sided 95% CI for the ratios of GMTs at 1 month after the third vaccination were entirely contained within the interval [0.74, 1.33], thereby meeting the criterion for lot consistency [0.50, 2.00]. • The lower limits of the two-sided 95% CI for the percentage of subjects with an hSBA ≥ 1:5 at 1 month following the third vaccination were: 100% against the H44/76 and 5/99 strains, and 84% against the NZ98/254 strain, thereby meeting the sufficient immune response criterion.
V72P13E1 **Phase 3**	• Demonstration of a sufficient immune response following a fourth dose of BEXSERO administered at 12 months of age, either with or without concomitant Priorix-Tetra vaccination, to children (less than 2 years of age) previously primed with three doses of BEXSERO as	• The fourth dose immune response was considered sufficient if for the percentage of subjects with hSBA ≥1:5, the lower limit of the two-sided 95% CI was ≥75% for all 3 reference strains H44/76, NZ98/254 and 5/99.	Objectives were met. • For strains H44/76 and 5/99, 100% of the subjects had hSBA ≥1:5. The lower limit of the two-sided 95% CI was 98% in subjects with or without concomitant Priorix-Tetra vaccination. • For strain NZ98/254, 97% and 94% of the subjects in the vaccination groups had hSBA

Study	Primary Immunogenicity Objectives	Prospectively Defined Criterion	Outcome
	infants in Study V72P13.		≥1:5. The lower limit of the two-sided 95% CI was 93% in subjects with concomitant Priorix-Tetra and 90% in subjects without concomitant Priorix-Tetra vaccination.
V72_41 **Phase 3**	• Demonstration of the equivalence of rMenB+OMV NZ lot 1 to rMenB+OMV NZ lot 2 when administered to adolescents, as measured by hSBA GMTs for strains H44/76, 5/99, and NZ98/254 and ELISA GMCs against vaccine antigen 287-953 approximately 30 days after a primary vaccination course of two doses administered one month apart.	• The equivalence was considered a success if, at one month following the second vaccination, the two-sided 95% confidence interval (CI) of the ratio of the hSBA GMTs for each of 3 serogroup B reference strains (H44/76, 5/99, and NZ98/254) and the two-sided 95% CI of the ratio of the ELISA GMCs against vaccine antigen 287-953 are contained within the interval (0.5, 2.0).	Objective was met. • The ratios of hSBA GMTs in Lot 1_Rosia to Lot 2_Siena at one month after the second vaccination were 1.0, 0.92, and 0.81 for strains H44/76, 5/99, and NZ98/254, respectively, with corresponding two-sided 95% confidence intervals of (0.82, 1.23), (0.77, 1.10), and (0.60, 1.09). • The ratio of ELISA GMCs against vaccine antigen 287-953 at one month after second vaccination was 0.83, with a corresponding two-sided 95% CI of (0.67, 1.02).

CI: confidence interval;
GMT: geometric mean titers
hSBA: serum bactericidal assay using human complement

Immunogenicity Data

The primary immunogenicity measure was the proportion of subjects with human serum bactericidal assay (hSBA) equal to or above the threshold of 1:4 against each of the meningococcal serogroup B reference strains. This threshold, used in early-stage clinical studies (V72P6, V72P9, V72P4, V72P5 and V72P10) and in their extensions (V72P6E1, V72P9E1, V72P10E1), is an accepted correlate of protection. A threshold of 1:5 was then set after hSBA assay validation to ensure, based on the intermediate precision of the assay, 95% certainty of a true response of 1:4, and this cutoff was used to define seropositive responses in late-stage clinical studies V72P12, V72P12E1, V72P13, V72P13E1, V72P13E2, V72P16, V72_41.

Immunogenicity was evaluated in randomized, multicenter, clinical trials that enrolled infants, children (less than 2 years of age), adolescents and adults.

In infant study V72P13, participants received three doses of BEXSERO at 2, 4 and 6 months of age. In infant study V72P12, participants received three doses of BEXSERO at either 2, 4 and 6 or 2, 3, and 4 months of age. In infant study V72P16, participants received four doses of BEXSERO at 2, 3, 4 and 12 months of age. Sera were obtained both before vaccination and one month after the third vaccination (Table 13). Subjects who received three doses of BEXSERO in V72P12 and V72P13 received a fourth dose at either 12 months of age in the extension studies V72P12E1 and V72P13E1 (Table 14) or 18 and 24 months of age in study V72P12E1. In studies V72P16, V72P12E1 and V72P13E1 sera were obtained before and one month after the fourth vaccination.
Previously unvaccinated children (less than 2 years of age) in the above mentioned studies received 2 doses in the second year of life (Table 15). The immunogenicity after two doses has been also documented in another study in infants (V72P9) aged 6 months at enrolment (Table 15).

Vaccine-naive children enrolled in studies V72P6E1, V72P9E1 and V72P13E2 received two doses of BEXSERO with a two month-interval between doses. Sera were obtained both before vaccination and one month after the second vaccination.

In the adolescents studies, participants received two doses of BEXSERO with a one month (V72_41) or one, two or six month (V72P10)-interval between doses, as shown in Table 16. Sera were obtained both before vaccination and one month after each vaccination.

In other studies in adults (V72P4 and V72P5), data were also obtained after two doses of BEXSERO with a one month or two month interval between doses (Table 16). Sera were obtained both before vaccination and one month after each vaccination.

Immunogenicity in infants 2 months to 6 months of age

Immunogenicity results at one month after three doses of BEXSERO administered at 2, 3, 4 and

2, 4, 6 months of age are summarized in Table 13.
Persistence and data after a fourth dose administered at 12 months of age (following administration at 2, 3, 4 months of age in Study V72P12E1 and at 2, 4, 6 months of age in Study V72P13E1) are summarized in Table 14.

Baseline Geometric Mean Titers (GMT) were uniformly low against all strains in the BEXSERO (ranging from 1.02 to 1.49 for fHbp, NadA and PorA P1.4 antigens and from 3.15 to 3.51 for NHBA) and the control groups (ranging from 1.01 to 1.28 for fHbp, NadA and PorA P1.4 antigens and was 3.91 for NHBA) across studies. The responses one month after the third vaccination at a 2, 4, 6-month schedule were high against all antigens in the BEXSERO groups (Table 13). In contrast, the mean hSBA GMTs remained low and similar with respect to the baseline in the control groups (ranging from 1.04 to 1.25).

Table 13 - 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[a] (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[a] (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[a] (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[a] (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)

[a] % seropositive = the percentage of subjects who achieved an hSBA ≥ 1:5
hSBA = Serum Bactericidal Assay using human complement
GMT = Geometric Mean Titer.

As compared with study V72P13 (2, 4, 6- month schedule), percentages of subjects with hSBA ≥1:5 against NHBA and GMTs against NHBA, NadA and PorA P1.4 were significantly lower in study V72P12 and V72P16 (2, 3, 4- month schedule) at one month after the third vaccination.

A modest response was demonstrated following vaccinations with BEXSERO at the 2, 3, 4-month schedule in studies V72P12 and V72P16 as the percentages of subjects with hSBA ≥1:5 against NHBA was 36% vs. 6%; 43% vs. 20% for the BEXSERO vs. control groups, respectively.

The antibodies against PorA and fHbp rapidly declined in infants 6 and 12 months after the third dose, respectively. However a booster response was observed following a fourth vaccine dose administered during the second year of life, consistent with adequate priming with a three-dose primary series.

Table 14 - Serum Bactericidal Antibody Responses Following a Booster at 12 Months 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[a] % seropositive[b] (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[b] (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[b] (95% CI) hSBA GMT (95% CI)	-	N=299 62% (56-67) 6.5 (5.63-7.5)
NadA	pre-booster[a] % seropositive[b] (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[b] (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[b] (95% CI) hSBA GMT (95% CI)	-	N=298 97% (95-99) 81 (71-94)
PorA P1.4	pre-booster[a] % seropositive[b] (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[b] (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[b] (95% CI) hSBA GMT (95% CI)	-	N=300 17% (13-22) 1.91 (1.7-2.15)
NHBA	pre-booster[a] % seropositive[b] (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[b] (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[b] (95% CI) hSBA GMT (95% CI)	-	N=291 36% (31-42%) 3.35 (2.88-3.9)

[a] 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.
[b] % seropositive = the percentage of subjects who achieved an hSBA $\geq$ 1:5
hSBA = Serum Bactericidal Assay using human complement

GMT = Geometric Mean Titer

Concomitant use of BEXSERO with routine vaccines

Concomitant administration of BEXSERO was studied 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, and varicella.

Clinical study V72P12 demonstrated that the percentage of subjects with hSBA ≥1:5 for strain NZ98/254 was lower in the group that concomitantly administered BEXSERO and the routine vaccines (combined DTaP-IPV-HBV/Hib vaccine and heptavalent pneumococcal conjugate vaccine) than the group where they were administered separately at 1 month after the third dose. When administered alone, BEXSERO also elicited higher hSBA GMTs for all strains as compared to the concomitant group. The clinical implication of these differences remains unknown.

Inconsistent results were seen across studies for responses to inactivated poliovirus type 2 and pneumococcal conjugate serotype 6B; lower antibody titers to the pertussis pertactin antigen were also noted.
In addition, concomitant use of BEXSERO and MMRV demonstrated non-inferiority of seroconversion (≥ 1.25 gpELISA units/mL), but not of seroprotection (≥ 5 gpELISA units/mL) for varicella after the first dose, although the difference between the groups was only 2% (95% CI, -11%, 7%). The clinical implication of these differences remains unknown.

In a clinical trial, prophylactic use of acetaminophen had no impact on the immune responses of BEXSERO and for most antigens in routine vaccines after the primary series. These data do not suggest any clinically significant interference also considering that no impact was observed on the immune responses after the booster doses.

Immunogenicity in infants aged 6 to 11 months, children aged 12 to 23 months and 2 through 10 years of age

The immunogenicity after two doses in infants and children has been documented in three studies whose results are summarized in Table 15.

Baseline GMTs were uniformly low against all three strains in the studies in 6 to 11 and 12 to 23 months of age (ranging from 1.00 to 1.70) and increased following vaccination. The increase in hSBA titers for vaccine antigens was similar in additional groups of children following BEXSERO vaccination at 12-14 and 18-20 months of age. In these additional groups a similar response was also observed in terms of percentages of seropositive subjects (100% against fHbp antigen; 98-100% against NadA antigen; 93-99% against PorA P1.4 antigen; 74-86% against NHBA antigen).

In 24 to 26 months old children baseline GMTs were also low (ranging from 1.01 to 2.32 across all vaccine antigens). Additional data relative to the administration of two BEXSERO doses 2 months apart in children at 40-42 and 60-62 months of age (Studies V72P6E1, V72P9E1) were in line with the responses presented in Table 15.

Table 15 - Serum Bactericidal Antibody Responses Following BEXSERO Vaccination at 6 and 8 Months of Age (V72P9), 13 and 15 Months of Age (V72P13E1) or 24 and 26 Months of Age (V72P13E2) and Persistence of Bactericidal Antibody One Year After the Two Doses at 13 and 15 Months of Age (V72P13E2)

Antigen		Age range		
		6 to 11 months of age	**12 to 23 months of age**	**2 to 10 years of age**
		Age of vaccination		
		6, 8 months	**13, 15 months**	**24, 26 months**
fHbp	1 month after 2nd dose % seropositive[a] hSBA GMT	N=23 100% 250	N=163 100% (98-100)[b] 271 (237-310)[b]	N=105 100% (97-100)[b] 220 (186-261)[b]
	12 months after 2nd dose % seropositive[a] hSBA GMT	-	N=68 74% (61-83)[b] 14 (9.4-20)[b]	-
NadA	1 month after 2nd dose % seropositive[a] hSBA GMT	N=23 100% 534	N=164 100% (98-100)[b] 599 (520-690)[b]	N=103 99% (95-100)[b] 455 (372-556)[b]
	12 months after 2nd dose % seropositive[a] hSBA GMT	-	N=68 97% (90-100)[b] 70 (47-104)[b]	-
PorA P1.4	1 month after 2nd dose % seropositive[a] hSBA GMT	N=22 95% 27	N=164 100% (98-100)[b] 43 (38-49)[b]	N=108 98% (93-100)[b] 27 (23-32)[b]
	12 months after 2nd dose % seropositive[a] hSBA GMT	-	N=68 18% (9-29)[b] 1.65 (1.2-2.28)[b]	-
NHBA	1 month after 2nd dose % seropositive[a] hSBA GMT	-	N=46 63% (48-77)[b] 11 (7.07-16)[b]	N=100 97% (91-99)[b] 38 (32-45)[b]
	12 months after 2nd dose % seropositive[a] hSBA GMT	-	N=65 38% (27-51)[b] 3.7 (2.15-6.35)[b]	-

[a] % seropositive = the percentage of subjects who achieved an hSBA ≥ 1:4 (in the 6 to 11 months range of age) and hSBA ≥ 1:5 (in the 12 to 23 months and 2 to 10 years ranges of age).

[b] 95% Confidence Intervals are reported in brackets only for data generated from clinical studies V72P13E1 and V72P13E2 in the age range 12 to 23 months and 2 to 10 years of age.

hSBA = Serum Bactericidal Assay using human complement

GMT = Geometric Mean Titer.

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

The immunogenicity data of two doses administered with an interval of one, two or six months both in adults (V72P4, V72P5) and in adolescents (V72P10, V72_41) are shown in Table 16. Baseline GMTs ranged from 2.61 to 4.11 in adolescents and from 1.71 to 4.06 in adults against fHbp, NadA and PorA P1.4 antigens. Baseline GMTs against NHBA antigen ranged from 30 to 32 in adolescents (V72P10).

Table 16 - Serum Bactericidal Antibody Responses in Adolescents or Adults One Month After Two Doses of BEXSERO Administered According to Different Two-Dose Schedules

Antigen		**Adolescents**				**Adults**	
		V72_41 0, 1 months	**V72P10 0, 1 months**	**V72P10 0, 2 months**	**V72P10 0, 6 months**	**V72P5 0, 1 months**	**V72P4 0, 2 months**
fHbp	% seropositive[a]	N=298 99% (98-100)[b]	N=638 100% (99-100)[b]	N=319 100% (99-100)[b]	N=86 100% (99-100)[b]	N=28 100%	N=46 100%
	hSBA GMT	117 (105-130)[b]	210 (193-229)[b]	234 (209-263)[b]	218 (157-302)[b]	100	93
NadA	% seropositive[a]	N=299 100% (99-100)[b]	N=639 100% (99-100)[b]	N=320 99% (98-100)[b]	N=86 99% (94-100)[b]	N=28 100%	N=46 100%
	hSBA GMT	179 (163-197)[b]	490 (455-528)[b]	734 (653-825)[b]	880 (675-1147)[b]	566	144
PorA P1.4	% seropositive[a]	N=298 75% (70-80)[b]	N=639 100% (99-100)[b]	N=319 100% (99-100)[b]	N=86 100% (96-100)[b]	N=28 96%	N=46 91%
	hSBA GMT	10 (8.77-12)[b]	92 (84-102)[b]	123 (107-142)[b]	140 (101-195)[b]	47	32
NHBA	% seropositive[a]	-	N=46 100% (92-100)[b]	N=46 100% (92-100)[b]	-	-	-
	hSBA GMT	-	99 (76-129)[b]	107 (82-140)[b]	-	-	-

[a] % seropositive = the percentage of subjects who achieved an hSBA ≥ 1:4 (in clinical studies V72P5, V72P4, and V72P10) and hSBA ≥ 1:5 (in clinical study V72_41).
[b] 95% Confidence Intervals are reported in brackets only for clinical studies V72P10 and V72_41.
hSBA = Serum Bactericidal Assay using human complement.
GMT = Geometric Mean Titer.

In study V72P10, subjects were stratified by pre-vaccination titer baseline hSBA <1:4 or ≥1:4. The percentage of subjects with at least a 4-fold increase in hSBA titer from baseline one month after the last dose of BEXSERO is summarized in Table 17.

Table 17 - 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[a] (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 (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[a] (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)
	% 4-fold increase (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[a] (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 (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[a] (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 (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)	-

[a] % seropositive = the percentage of subjects who achieved an hSBA ≥ 1:4

DETAILED PHARMACOLOGY

Duration of Effect

The data on duration of immune status is not yet established.

TOXICOLOGY

Table 18 - Nonclinical Toxicology Studies

Study type, gender, and species	Route and regimen	Results
Single and repeat dose toxicity and local tolerability, male and female rabbits	One or five 0.5 mL or 1 mL intramuscular doses of rMenB±OMV [d](50 µg or 100 µg of each recombinant protein NHBA, NadA and fHbp[a], and 25 µg of OMV NZ or NW in 1.5 mg or 3 mg $Al(OH)_3$) two weeks apart for eight weeks	No systemic adverse effects and well tolerated locally
Pilot reproductive & developmental toxicity female rabbits	Five 0.5 mL or 1 mL intramuscular doses of rMenB±OMV[d] approx. two weeks apart. Three doses before mating and two during gestation (1× dose in 0.5 mL: 50 µg of each recombinant protein NHBA, NadA and fHbp[a], 25 µg of OMV NZ in 1.5 mg $Al(OH)_3$; or 2× dose in 1 mL, administered 0.5 mL in each leg)	No systemic toxicity in maternal rabbits and no teratogenic effects
Pivotal reproductive & developmental toxicity female rabbits	Five 0.5 mL intramuscular doses of rMenB±OMV[d] two weeks apart. Three doses before mating and two during gestation (50 µg of each recombinant protein NHBA, NadA and fHbp[a], 25 µg of OMV NZ in 1.5 mg $Al(OH)_3$)	No systemic toxicity in maternal rabbits and no reproductive, embryofetal, or postnatal developmental effects
In vitro toxicity non-GLP studies in human cells	HBMEC, HUVEC cells[b], human plasma or whole blood and platelet-rich plasma treated with vaccine components at various incubation times	No effects on cytotoxicity, binding to human cells, cytokines production, coagulation[c], platelet activation, platelet-leukocyte aggregation
Single and repeat dose toxicity and local tolerability male and female rabbits	One or five 0.5 mL intramuscular doses of MenB protein 287±OMV (50 µg MenB recombinant 287 ± 25 µg OMV in 1.65 mg $Al(OH)_3$) two weeks apart	No systemic adverse effects and well tolerated locally
Reproductive & developmental toxicity female rabbits	Eight 0.5 mL intramuscular doses of MeNZB™. Three doses two weeks apart before mating and five doses every 3 to 4 days during gestation (25 µg OMV in 0.5 mL with 1.65 mg $Al(OH)_3$ before mating; 6.25 µg, 25 µg or 50 µg OMV in 0.13 to 1 mL with $Al(OH)_3$ during gestation)	No systemic toxicity in maternal rabbits and no teratogenic effects

[a] proteins NHBA, NadA and fHbp also named antigens 287-953, 961c, and 936-741;
[b] human umbilical vein endothelial cells and human brain microvascular endothelial cells;
[c] PT, PTT and activated Protein C;
PT: prothrombin time;
PTT: partial thromboplastin time;
[d] rMenB+OMV NZ corresponds to BEXSERO

REFERENCES

1. Canada Communicable Diseases Report. (2013) Update on the Invasive Meningococcal Disease and Meningococcal Vaccine Conjugate Recommendations Volume 39, ACS-1, January 2013.

2. Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R. The Disease Burden of Invasive Meningococcal Serogroup B Disease in Canada. Pediatr Infect Dis J 2013;32: e20–e25.

3. Gilca R, Deceuninck G, Lefebvre B, Tsang R, Amini R, et al. (2012) The Changing Epidemiology of Meningococcal Disease in Quebec, Canada, 1991–2011: Potential Implications of Emergence of New Strains. PLoS ONE 7(11): e50659. doi:10.1371/journal.pone.0050659.

4. Donnelly, Medini D, Boccadifuoco G, Biolchi A, Ward J et al. Qualitative and quantitative assessment of meningococcal antigens to evaluate the potential strain coverage of protein-based vaccines. Proc Natl Acad Sci U S A 2010; 107(45):19490-5

5. Julie A. Bettinger, David W. Scheifele, Scott A. Halperin, Wendy Vaudry, Jamie Findlow, Ray Borrow, Duccio Medini, Raymond Tsang, For the members of the Canadian Immunization Monitoring Program, Active (IMPACT), Diversity of Canadian meningococcal serogroup B isolates and estimated coverage by an investigational meningococcal serogroup B vaccine (4CMenB), Vaccine, Available online 12 April 2013, ISSN 0264-410X, http://dx.doi.org/10.1016/j.vaccine.2013.03.063.

6. National Advisory Committee on Immunization (NACI) (2009). Update on the invasive meningococcal disease and meningococcal vaccine conjugate recommendations. Canada Communicable Disease Report, 36(ACS-3)

7. National Advisory Committee on Immunization (NACI) (2009). Statement on meningococcal vaccination for travellers. Canada Communicable Disease Report, 35(ACS-4): 1–22.

8. Goldschneider I., et. al. (1969b) Human immunity to the meningococcus. II. Development of natural immunity. J Exp Med (6):1327-1348.

9. Goldschneider I., et. al. (1969a) Human immunity to the meningococcus. I. The role of humoral antibodies. J Exp Med (6):1307-26.

10. Holst, J. et al. (2013) Vaccines against meningococcal serogroup B disease containing outer membrane vesicles (OMV): Lessons from past programs and implications for the future. Hum Vaccin Immunother. 2013 Mar 7;9(6).

11. Borrow, R., et al. (2006) Neisseria meningitidis group B correlates of protection and assay

standardization—International Meeting Report Emory University, Atlanta, Georgia, United States, 16–17 March 2005. Vaccine 24:5093-5107.

12. Feavers I, Griffiths E, Baca-Estrada M, et al. WHO/Health Canada meeting on regulatory considerations for evaluation and licensing of new meningococcal Group B vaccines, Ottawa, Canada, 3-4 October 2011. Biologicals. 2012;40(6):507-16).

PART III: CONSUMER INFORMATION

BEXSERO®

Multicomponent Meningococcal B Vaccine (recombinant, adsorbed)

This leaflet is Part III of a three-part "Product Monograph" published when BEXSERO was approved for sale in Canada and designed specifically for consumers. This leaflet is a summary and will not tell you everything about BEXSERO. Contact your doctor/pharmacist/nurse if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is used for:

BEXSERO is a vaccine for the prevention of Meningococcal disease caused by the *Neisseria meningitidis* group B bacteria (germs). These germs can cause serious, and sometimes life‑threatening, infections such as meningitis (infection of the lining of the brain and spinal cord) and sepsis (blood poisoning). BEXSERO is given to individuals from 2 months through 17 years of age.

What it does:

The vaccine works by specifically stimulating the immune system of the vaccinated person, causing the production of substances in the blood called antibodies. The antibodies kill the germ that causes meningococcal disease, *N. meningitidis.* If a vaccinated person is infected by *N. meningitidis*, their immune system is usually ready to destroy it.

When it should not be used:

If you or your child are allergic (hypersensitive) to the active substances or any of the other ingredients of BEXSERO

What the medicinal ingredients are:

The active substances are:
50 µg of recombinant *Neisseria meningitidis* group B NHBA fusion protein
50 µg of recombinant *Neisseria meningitidis* group B NadA protein
50 µg of recombinant *Neisseria meningitidis* group B fHbp fusion protein
25 µg of Outer Membrane Vesicles *Neisseria meningitidis* group B strain NZ98/254

Antigens are adsorbed on aluminum hydroxide (0.5 mg aluminum).

What the important nonmedicinal ingredients are:

Sodium chloride, histidine, sucrose, water for injections.

For a full listing of non- medicinal ingredients, see Part I of the Product Monograph.

What dosage forms are available?

Each dose of 0.5 mL is a suspension for intramuscular injection provided in a prefilled glass (Type I) syringe. Syringes are available in packages containing either one or ten syringes, supplied with or without needles.

WARNINGS AND PRECAUTIONS

BEFORE you or your child receive BEXSERO, talk to your doctor/pharmacist/nurse if:

- you or your child have a severe infection with a high temperature. If this is the case, then vaccination will be postponed. The presence of a minor infection, such as a cold, should not require postponement of the vaccination, but talk to your doctor/pharmacist/nurse first.
- you are pregnant or breast feeding, think you may be pregnant or are planning to have a baby, ask your doctor/pharmacist/nurse for advice before BEXSERO is given.
- you have hemophilia or any other condition that may slow down the clotting of your blood, such as treatment with blood thinners (anticoagulants).
- you or your child have an allergy to the antibiotic kanamycin. If present, the kanamycin level in the vaccine is low. If you or your child may have allergy to kanamycin, talk to your doctor/pharmacist/nurse first.

Fainting, feeling faint or other stress-related reactions can occur as a response to any needle injection. Tell your doctor or nurse if you have experienced this kind of reaction previously.

Tell your doctor/pharmacist/nurse if you know that you or your child is allergic to latex. The tip cap of the syringe may contain natural rubber latex. Although the risk for developing allergic reactions is very small, your doctor/pharmacist/nurse should consider the benefit-risk prior to administering this vaccine to subjects with known history of hypersensitivity to latex.

Your doctor/pharmacist/nurse may ask you to give your child medicines that lower fever at the time and after BEXSERO has been given. This will help to reduce some of the side effects of BEXSERO.

There are no data on the use of BEXSERO in patients with chronic medical conditions or with weakened immunity. If you or your child have weakened immunity (for example, due to the use of immunosuppressive medications, or HIV infection, or hereditary defects of the body's natural defense system), it is possible that the effectiveness of BEXSERO is reduced.

As with any vaccine, BEXSERO may not fully protect all of those who are vaccinated.

BEXSERO is not expected to provide protection against all circulating meningococcal serogroup B strains.

BEXSERO has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section "Side effects and what to do about them" may temporarily affect the ability to drive or use machines.

INTERACTIONS WITH THIS VACCINE

Tell your doctor/pharmacist/nurse if you or your child are taking, have recently taken, or might take any other medicines, or have recently received any other vaccine.
BEXSERO can be given at the same time as any of the following vaccine antigens, either as monovalent or as combination vaccines: diphtheria, tetanus, acellular pertussis (whooping cough), *Haemophilus influenzae* type b, inactivated polio, hepatitis B, heptavalent pneumococcal conjugate, measles, mumps, rubella, and chickenpox. Talk to your doctor/pharmacist/nurse for further information.

When BEXSERO is given at the same time as any other vaccine, the vaccines must be given at separate sites.

PROPER USE OF THIS VACCINE

Usual dose:
Your doctor/pharmacist/nurse will inject the recommended dose (0.5 mL) of the vaccine into your or your child's arm or leg muscle.
BEXSERO must not be mixed with any other vaccine or medicinal products in the same syringe.

Infants aged 2 months through 5 months
Your child should receive an initial course of three injections of the vaccine followed by a fourth dose.
The interval between vaccinations should be at least 1 month.
A fourth vaccination is required in the second year of life between 12 and 23 months of age. It is preferred this dose be given early in the second year of life, whenever possible.

Unvaccinated infants aged 6 months through 11 months
Infants aged 6 through 11 months should receive two injections, given at least 2 months apart. A third injection is required in the second year of life, after an interval of at least 2 months from the last dose. The need for further injections has not been established.
Unvaccinated children aged 12 months through 23 months
Children aged 12 through 23 months should receive two injections, given at least 2 months apart. The need for further injections has not been established.

Children aged 2 years through 10 years
Children aged 2 through 10 years should receive two injections, given at least 2 months apart. The need for a third injection has not been established.

Individuals aged 11 years through 17 years
Individuals aged 11 through 17 years of age should receive two injections. The interval between each injection should be at least 1 month. The need for a third injection has not been established.
Make sure that you or your child gets all doses. This allows you or your child to get the full benefits of BEXSERO.
Overdose:

In case of vaccine overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to go back to the doctor/pharmacist/nurse at the scheduled time ask the doctor/pharmacist/nurse for advice.

If you have any further questions on the use of BEXSERO, ask your doctor/pharmacist/nurse.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all vaccines, BEXSERO can cause side effects, although not everybody gets them.
When BEXSERO is given to you or your child, the very common side effects (may affect more than 1 in 10 people) that you or your child may get (reported in all age groups) are:
- pain/tenderness at the injection site, redness of the skin at the injection site, swelling of the skin at the injection site, hardness of the skin at the injection site.

The following side effects may also occur after receiving this vaccine.

Infants and children (up to 10 years of age)
Very common (these may affect more than 1 in 10 people)
- fever (≥38ºC)
- loss of appetite
- tenderness or discomfort at the injection site (including severe injection site tenderness resulting in crying when injected limb is moved)
- skin rash (uncommon after booster)
- sleepiness
- feeling irritable
- unusual crying
- vomiting
- diarrhea

Uncommon (these may affect up to 1 in 100 people)
- high fever (≥40°C)
- seizures (including febrile seizures)
- vomiting (after booster)
- dry skin, itchy rash, skin rash
- paleness (rare after booster)

Rare (these may affect up to 1 in 1,000 people)

- Kawasaki disease which may include symptoms such as fever that lasts for more than five days, associated with a skin rash on the trunk of the body, and sometimes followed by a peeling of the skin on the hands and fingers, swollen glands in the neck, red eyes, lips, throat and tongue.

Individuals from 11 years of age and older
Very common (these may affect more than 1 in 10 people).

- pain at the injection site resulting in inability to perform normal daily activity
- painful muscles and joints
- nausea
- generally feeling unwell
- headache

Side effects that have been reported during marketed use include:

Allergic reactions that may include severe swelling of the lips, mouth, throat (which may cause difficulty in swallowing), difficulty breathing with wheezing or coughing, rash, loss of consciousness and very low blood pressure; feeling faint or fainting; blisters at or around the injection site.

If any of the noted side effects becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor/pharmacist/nurse immediately.

This is not a complete list of side effects. For any unexpected effects while taking BEXSERO, contact your doctor/pharmacist/nurse.

HOW TO STORE IT

Store in a refrigerator at 2°C to 8°C.
Do not freeze. Do not use vaccine that may have been frozen.
Protect from light.
Do not use BEXSERO after the expiry date.
Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

For health care professionals:
If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local health unit in your province/territory.

For the General Public:
Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada:

By toll-free telephone: 866-844-0018
By toll-free fax: 866-844-5931
Email: caefi@phac-aspc.gc.ca
Web: http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php

Mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road, A/L 6502A
Ottawa, ON K1A 0K9

NOTE: *Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.*

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.gsk.ca or by contacting the sponsor,

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