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 four *N. meningitidis* serogroup B 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 25 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, subcutaneously or intradermally.

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

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

There are limited 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 immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

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 individuals 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 individuals 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

Individuals with impaired immune responsiveness, whether due to the use of immuno-suppressive therapy, a genetic disorder, or other causes, may have reduced antibody response to

active immunisation. Immunogenicity data are available in individuals with complement deficiencies, and in individuals with splenic dysfunction or asplenia (see CLINICAL TRIALS).

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.

Adults:
Limited safety and immunogenicity data are available in individuals above 25 years of age. The safety and efficacy of BEXSERO in individuals above 50 years have not been established. See ADVERSE REACTIONS and CLINICAL TRIALS.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview
In clinical trials, the most frequent local and systemic adverse reactions after vaccination with BEXSERO were tenderness, erythema, induration, fever, irritability, unusual crying, sleepiness in infants and children (less than 2 years of age), and pain, erythema, induration, malaise, headache, myalgia in adolescents and adults. Higher rates of antipyretic use were also reported for infants vaccinated with BEXSERO and routine vaccines. When BEXSERO was given alone,

the frequency of fever was similar to that associated with routine infant vaccines administered during clinical trials. Most solicited reactions were mild or moderate in severity and transient. No increase in the incidence or severity of the adverse reactions was seen with subsequent doses of the vaccination series.

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 13 studies, including 9 randomized controlled clinical trials with 7526 participants (from 2 months of age) who received BEXSERO. Among BEXSERO recipients, 4843 were infants and children (less than 2 years of age), 1503 were adolescents (11 to 17 years of age) and 1180 were adults (above 17 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 for 988 infants and children (less than 2 years of age) and 594 children (2 to 10 years of age) exposed to BEXSERO in subsequent studies have additionally been evaluated.

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.

Infants and Children (less than 2 years of age)

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.

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.

Solicited Adverse Reactions

3+1 Infant Schedule

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 (≥ 38 °C) was more frequently reported following vaccination with BEXSERO concomitantly with routine vaccines, compared with meningococcal C conjugate vaccine (MENJUGATE) 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
	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

2+1 Infant Schedule

In an additional study, V72_28, the occurrence of solicited local and systemic reactions in infants vaccinated with the 3+1-dose schedule (Group I received 3 primary doses of BEXSERO at 2½, 3½ and 5 months, followed by a booster at 11 months of age) were similar to the 2+1-dose schedule (Group II received 2 primary doses of BEXSERO at 3½ and 5 months, followed by a booster at 11 months of age). There were no new significant safety signals in the 2+1 BEXSERO vaccination group (Group II), apart from that of the known safety profile from the 3+1 dose schedule.

Unsolicited Adverse Events

3+1 Infant Schedule

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 5.

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 5 - 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.

2+1 Infant Schedule

In an additional study, V72_28, the percentage of subjects with unsolicited adverse events in infants vaccinated with the 3+1 dose schedule (Group I received 3 primary doses of BEXSERO at 2½, 3½ and 5 months, followed by a booster at 11 months of age) were similar to the 2+1 dose schedule (Group II received 2 primary doses of BEXSERO at 3½ and 5 months, followed by a booster at 11 months of age).

Children (aged 2 years to 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 62 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.

Solicited Adverse Reactions

Data on local and systemic reactions following vaccination with BEXSERO in children 2 to 10 years of age are shown in Table 6 and Table 7. 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 6 - 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				
		24 to 26 months of age		40-44 months of age		60-62 months of age
Local Reaction	Study Dose	V72P12E1 (N=54)	V72P13E2 (N=112)	V72P6E1 (N=42)	V72P9E1 (N=41)	V72P9E1 (N=48)
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 7 - 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				
		24 to 26 months of age		40-44 months of age		60-62 months of age
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 Temp. ≥38°C (≥40°C)]	1	28 (0)	21 (0)	10 (0)	15 (3)	10 (0)
	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)

Unsolicited Adverse Events

Table 8 provides an overview of unsolicited adverse events collected up to month 62 in children 2 to 10 years of age.

Table 8 - 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				
	24 to 26 months of age		40-44 months of age		60-62 months of age
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 (aged 11 to 17 years)

The characterization of the safety profile of BEXSERO in the adolescent population aged 11 to 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.

Solicited Adverse Reactions

Data on local and systemic reactions are shown in Table 9.

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 9 - 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) 11-17 years of age**	
	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

Unsolicited Adverse Events

Table 10 provides an overview of unsolicited adverse events collected up to study Month 3 in adolescents who received BEXSERO in either the 0-1 month or 0-2 month schedule (study V72P10). 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 (11 to 17 Years of Age), 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	**11 to 17 yoa N=380**
Any AEs	43	46
Possibly or probably related AEs	17	16
Serious AEs	1	1

[a] 0-1 schedule: BEXSERO was administered 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 11 to 17 years of age (study V72P10);
yoa: years of age;
vs: versus;
AEs: Adverse Events.

Adults

The characterization of the safety profile of BEXSERO in the adult population (above 17 years of age) was based on data from 7 studies, V72_29, V72_37, V72_59, V72_74, V72P4, V72P5, and V102_03. Most of the subjects enrolled in the studies were between 18 and 24 years of age. In addition, there were 82 subjects 25 to 50 years of age and 3 subjects above 50 years of age. Two or three doses of BEXSERO were administered according to one of the following schedules: 0-1, 0-2, 0-1-2, or 0-2-6 months. The data supporting the safety and tolerability of the two-dose adult vaccination schedule were generated from data collected in the first and second doses, pooled across studies and stratified by age (18 to 24 years, and 25 years and older). Data on solicited local (pain, erythema, swelling and induration) and systemic (chills, nausea, malaise, myalgia, arthralgia, headache, fever, rash, fatigue, loss of appetite) reactions were collected in clinical studies on the day of vaccination and for the following 6 days after vaccination (days 1-7 after vaccination).

Solicited Adverse Reactions

Percentage of adults experiencing local and systemic reactions on days 1 to 7 following each vaccination with BEXSERO are presented in Table 11 and Table 12. The incidence rate of the individual solicited local and systemic adverse events in subjects 18 to 24 years was generally higher in the BEXSERO group than in the control group. After both vaccinations, the most commonly reported local adverse reactions were pain, followed by erythema. The most commonly reported systemic adverse reactions were myalgia and headache. Most of the subjects reported solicited local and systemic adverse reactions which were mild to moderate in severity. The most commonly reported severe solicited reactions were pain and myalgia. Limited data

from V72P4, V72P5, V72_59 and V102_03 in subjects above 25 years of age showed the same trend in the most commonly reported solicited local and systemic adverse events and the severity of the adverse events as in subjects 18 to 24 years.

Table 11 - Percentage of Adults (18 to 24 Years of Age) Experiencing Local Reactions on Days 1-7 Following Each Vaccination with BEXSERO, Pooled Across Studies, Two-Dose Schedules[a]

Percentages of Subjects[b] With Any (Severe[c]) Local Adverse Reactions					
Study		**Studies with control arm V72_29[d] + V102_03**		**Studies without control arm V72P4 + V72P5 + V72_59**	**Pooled across studies V72_29[d] + V72_59 + V72P4 + V72P5 + V102_03**
	Dose	**Control[e]**	**BEXSERO**	**BEXSERO**	**BEXSERO**
	1	**N = 402**	**N = 226**	**N = 12**	**N = 238**
	2	**N = 378**	**N = 216**	**N = 11**	**N = 227**
Pain	1st	46 (0)	93 (10)	92 (17)	93 (11)
	2nd	49 (1)	88 (10)	91 (0)	88 (10)
Erythema	1st	25 (0)	41 (<1)	42 (0)	41 (<1)
	2nd	19 (0)	41 (1)	27 (0)	40 (1)
Induration	1st	11 (0)	27 (1)	42 (0)	28 (<1)
	2nd	9 (0)	23 (0)	36 (0)	24 (0)
Swelling[b]	1st	8 (0)	25 (1)	0 (0)	25 (1)
	2nd	7 (<1)	26 (0)	0 (0)	26 (0)

Notes: Only unsolicited adverse event data were collected in studies V72_37 and V72_74. Solicited safety set: all subjects in the exposed set who provided postvaccination reactogenicity data.

[a] 0, 1 schedule: V72_29, V72P5. All other studies had a 0, 2 schedule. For studies V72P4 and V72P5 an additional dose was given i.e., 3 doses were given compared to 2 doses in the other studies. The third dose was not included in the post-hoc analyses.

[b] Swelling was solicited for V72_29 and V72_59, not solicited in V102_03, V72P4 or V72P5.

[c] Severe pain - unable to perform normal daily activity; severe erythema, induration and swelling - >100 mm.

[d] For study V72_29 solicited local and systemic AEs were collected only in the immunogenicity subset, while all unsolicited AEs and SAEs were collected for all study participants.

[e] For study V72_29, control group includes subjects that received IXIARO, as well as the Placebo/ACWY group where first vaccination was MenACWY, second vaccination was placebo. For study V102_03, control group includes subjects whose first vaccination was placebo, second vaccination was MenACWY.

Table 12 - Percentage of Adults (18 to 24 Years of Age) Experiencing Systemic Reactions on Days 1-7 Following Each Vaccination with BEXSERO, Pooled Across Studies, Two-Dose Schedules[a]

Percentages of Subjects With Any (Severe[b]) Systemic Adverse Reactions					
Study		**Studies with control arm V72_29[c] + V102_03**		**Studies without control arm V72P4 + V72P5 + V72_59**	**Pooled across studies V72_29[c] + V72_59 + V72P4 + V72P5 + V102_03**
	Dose	**Control[d]**	**BEXSERO**	**BEXSERO**	**BEXSERO**
	1	**N = 402**	**N = 226**	**N = 12**	**N = 238**
	2	**N = 379**	**N = 215**	**N = 11**	**N = 226**
Malaise[e]	1st	18 (1)	17 (1)	27 (0)	18 (<1)
	2nd	12 (1)	22 (2)	20 (0)	22 (2)
Nausea	1st	8 (<1)	13 (<1)	0 (0)	13 (<1)
	2nd	5 (1)	10 (<1)	9 (0)	10 (<1)
Myalgia	1st	45 (1)	70 (7)	33 (8)	68 (7)
	2nd	40 (1)	66 (7)	45 (0)	65 (6)
Arthralgia	1st	8 (<1)	12 (1)	25 (0)	13 (1)
	2nd	8 (1)	12 (1)	18 (0)	12 (1)
Headache	1st	27 (<1)	29 (1)	42 (0)	30 (1)
	2nd	17 (1)	22 (2)	27 (0)	22 (2)
Fever	1st	2 (0)	1 (0)	8 (0)	1 (0)
	2nd	1 (0)	2 (0)	0 (0)	2 (0)
Analgesic /antipyretic Use	1st	8 (-)	20 (-)	17 (-)	20 (-)
	2nd	6 (-)	23 (-)	0 (-)	21 (-)
Stayed home due to reaction	1st	2 (-)	3 (-)	27 (-)	4 (-)
	2nd	1(-)	6 (-)	20 (-)	7 (-)

Notes: Only unsolicited adverse event data were collected in studies V72_37 and V72_74. Solicited safety set: all subjects in the exposed set who provided postvaccination reactogenicity data.

[a] 0, 1 schedule: V72_29, V72P5. All other studies had a 0, 2 schedule. For studies V72P4 and V72P5 an additional dose was given i.e., 3 doses were given compared to 2 doses in the other studies. The third dose was not included in the post-hoc analyses.

[b] Severe: malaise = unable to perform daily activity; nausea = leading to minimal to no oral intake; myalgia, arthralgia, headache = prevented daily activity; fever ≥40°C.

[c] For study V72_29 solicited local and systemic AEs were collected only in the immunogenicity subset, while all unsolicited AEs and SAEs were collected for all study participants.

[d] For study V72_29, control group includes subjects that received IXIARO, as well as the Placebo/ACWY group where first vaccination was MenACWY, second vaccination was placebo. For study V102_03, control group includes subjects whose first vaccination was placebo, second vaccination was MenACWY.

[e] Malaise was solicited for V72_29, V72P4 and V72P5 only.

Unsolicited Adverse Events
Data on unsolicited AEs in adults (subjects 18 to 24 years) are shown in Table 13.

Table 13 - Overview of Unsolicited Adverse Events Reported Up to 3 Months in Adults, Pooled Across Studies, Two-Dose Schedules[a]

	Percentage of Subjects with Unsolicited Adverse Events
Study	**V102_03 + V72_29 + V72P4 + V72P5 + V72_59 + V72_74**
	BEXSERO N=1048
Any AE	25
Possibly or probably related AEs	7
SAEs	2

Abbreviation: AE, adverse event, SAE, serious adverse event.
Notes: Unsolicited safety set: all subjects in the exposed set who provided post vaccination unsolicited AE records.
[a] 0, 1 schedule: V72_29, V72P5. All other studies had a 0, 2 schedule. The reporting period here is up to 1 month following the second dose in a 0,2 dose schedule.

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
Fever (adolescents from 11 years of age and adults), injection site reactions (including extensive swelling of the vaccinated limb, blisters at or around the injection site and injection site nodule which may persist for more than one month)

Immune system disorders
Allergic reactions (including anaphylactic reactions)

Nervous system disorders
Hypotonic-hyporesponsive episode, syncope or vasovagal responses to injection

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, varicella, and meningococcal group C-CRM conjugate (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

Age at First Dose	Primary Doses	Intervals between Primary Doses	Booster
Infants, 2 months to 5 months	**3+1 schedule:**		
	Three doses each of 0.5 mL	Not less than 1 month	1 booster[1]
	2+1 schedule:		
	Two doses each of 0.5 mL	Not less than 2 months	1 booster[1]
Infants, 6 months to 11 months	Two doses, each of 0.5 mL	Not less than 2 months	1 booster[2]
Children, 12 months to 23 months	Two doses, each of 0.5 mL	Not less than 2 months	Need not established
Children, 2 years to 10 years	Two doses, each of 0.5 mL	Not less than 1 month	Need not established
Adolescents and Adults, 11 years through 25 years	Two doses, each of 0.5 mL	Not less than 1 month	Need not established

[1] In the second year of life with an interval of at least 6 months between the primary doses and booster.
[2] In the second year of life with an interval of at least 2 months between the primary doses and booster.

Infants aged 2 months to 5 months of age at the time of first dose
The vaccination schedule consists a total of three or four doses, each of 0.5 mL. It consists of two or three primary doses. The interval between vaccinations should be at least 2 months if two primary doses are given or at least 1 month if three primary doses are given. A booster will be given in the second year of life with an interval of at least 6 months between the primary series and booster dose. It is preferred this dose be given early in the second year of life, whenever possible.

Infants aged 6 months to 11 months of age at the time of first dose
The vaccination schedule consists a total of three doses, each of 0.5 mL. It consists of two primary doses, given not less than 2 months between doses, followed by a booster in the second year of life with an interval of at least 2 months between the primary doses and the booster. The need for further booster doses has not been established.

Children aged 12 months to 23 months of age at the time of first dose
The vaccination schedule consists of two primary doses, each of 0.5 mL, given not less than 2 months between doses. The need for a booster dose after this vaccination schedule has not been established.

Children aged 2 years to 10 years of age at the time of first dose
The vaccination schedule consists of two primary doses, each of 0.5 mL, given not less than 1 month between doses. The need for a subsequent dose after this vaccination schedule has not been established.

Adolescents and Adults aged 11 years through 25 years of age at the time of first dose
The vaccination schedule consists of two primary doses, each of 0.5 mL, given not less than 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 individuals.

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

Neisseria meningitidis is the bacterium which causes invasive meningococcal disease (IMD), an important cause of meningitis and septicaemia. Strains of *N. meningitidis* can be classified into 12 distinct serogroups based on the composition of their distinct polysaccharide capsules. Of the known serogroups, only 4 (B, C, W-135 and Y) are responsible for the vast majority of IMD within Canada. Following the implementation of meningococcal conjugate C immunization programs in Canada, and the corresponding decline in serogroup C IMD, serogroup B has become the leading cause of IMD.

From 2007-2011, the average annual number of IMD cases in Canada was close to 200 (range: 154 to 229) (13). In the general population, approximately 60% of IMD cases have been attributed to serogroup B, with the greatest disease burden seen in young infants (<1 years) and children 1-4 years of age (13). A secondary peak of incidence occurs in adolescents and young adults 15-19 years of age (13). Pharyngeal carriage rates of meningococci are highest in the adolescent population and range from 20-30%. A large proportion of IMD cases in individuals 20 years of age and above are also due to serogroup B (~40%) (13). The case-fatality rates due to IMD vary by serogroup and age, and approximate 9% in Canada. IMD has one of the highest CFRs of any vaccine-preventable disease and those who survive can face significant life-long sequalae. Sequelae were reported in 19% of serogroup B cases (14). These results highlight both the significant mortality and morbidity, associated with IMD in general, and serogroup B specifically.

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), https://www.canada.ca/en/public-health/services/publications/healthy-living/meningococcal-serogroup-b-vaccine-advice.html.

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 Epidemiology Data).

Pharmacodynamics

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).

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 (mcg)
Recombinant *Neisseria meningitidis* serogroup B NadA protein[1, 2, 3]	50 micrograms (mcg)
Recombinant *Neisseria meningitidis* serogroup B fHbp fusion protein[1, 2, 3]	50 micrograms (mcg)
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 (mcg)

[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).

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 are based on data from 15 clinical studies (see Table 14).

Table 14 - 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)
Infants and Children (2 months to 10 years of age)						
V72P12 Phase 2b	2 mos	Open-label, multicenter, randomized, controlled Safety, immunogenicity, schedule finding	0.5 mL, 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	0.5 mL, 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 consistency	0.5 mL, IM Schedule: 2, 4, 6 mos of age	3630 (2480)	73.5 (54-132) days	51%
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	0.5 mL, 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	0.5 mL, 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%

Table 14 (con'td) - 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)
Infants and Children (2 months to 10 years of age) (cont'd)						
V72P16 Phase 2	2 mos	Partially observer-blind, randomized, controlled, multicenter dose-ranging and formulation-finding Safety and immunogenicity	0.5 mL, IM Schedule: 2, 3, 4, 12 mos of age	1507 (736)	74.6 (54-91) days	54%
V72P9 Phase 2	6-8 mos	Single-blind, single center, randomized Safety, immunogenicity of infant primary series + third dose	0.5 mL, IM Schedule: 6, 8, 12 mos of age	60 (30)	7.1 (6-8) mos	47%
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	0.5 mL, 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%
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	0.5 mL, 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%

Table 14 (con'td) - 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)
Infants and Children (2 months to 10 years of age) (cont'd)						
V72_28 Phase 3	2 mos-8 yrs	Open-label, multicenter, safety, tolerability and immunogenicity	0.5 mL, IM Schedules: Group I[b]: 2½, 3½, 5 + booster at 11 months of age Group II[b]: 3½, 5 + booster at 11 months of age Group III[b]: 6, 8 mos + booster at 11 months of age Group IV[c]: 0, 2 mos Group V[d]: 3, 5, 7, 12 mos Group VI[d]: 3, 5, 7, 12, 13, 15 mos	Group I: 253 (252) Group II:250 (249) Group III: 251 (250) Group IV: 404 (404) Group V: 126 (126) Group VI: 125 (124)	Group I: 2 mos Group II: 3 mos Group III: 6 mos Group IV: 7 yrs Group V: 3 mos Group VI: 3 mos	Group I: 54% Group II: 50% Group III: 49% Group IV: 51% Group V: 41% Group VI: 53%
V72_28E1 Phase 3	35 mos – 12 yrs	Open label, multicenter extension study of Study V72_28.	0.5 mL, IM Group I-III: Vaccinated cohort: subjects from Groups I-III of Study V72_28 receiving 1 dose 24-36 mos later. Group IVa and IVb: Vaccinated cohort: subjects from Group IV of Study V72_28 receiving 1 dose 24-36 mos later.	Group I vaccinated: 98 (97) Group 1 non-vaccinated: 47 (n.a) Group II vaccinated: 89 (89), non-vaccinated: 43 (n.a) Group III, vaccinated: 81 (80); non-vaccinated: 39 (n.a) Group IVa, vaccinated: 32 (32); non-vaccinated 36 (n.a) Group IVb, vaccinated: 91 (91); non-vaccinated: 90 (n.a)	Groups I-III: 35-47 months of age Group IVa: approximate age range 4-7 years of age (i.e 24-36 months after Study V72_28) Group IVb: approximate age range 8-12 years of age (i.e 24-36 months after Study V72_28)	Group I vaccinated: 55% Group 1 non-vaccinated: 43% Group II vaccinated: 46%, non-vaccinated: 49% Group III, vaccinated: 57%; non-vaccinated: 41% Group IVa, vaccinated: 41%; non-vaccinated 58% Group IVb, vaccinated: 52%; non-vaccinated: 49%

Table 14 (con'td) - 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)
Infants and Children (2 months to 10 years of age) (cont'd)						
V72_62 Phase 3	2-17 yrs	Open-label, controlled, multicenter, safety, tolerability and immunogenicity	0.5 mL, IM Schedule: 0, 2 mos	239 (n.a.)	10.3 (2-17) yrs	55%
Adolescents and Adults (11 years through 25 years of age)						
V72P10 Phase 2b/3	11-17 yrs	Observer-blind, multicenter, randomized, placebo controlled Safety, immunogenicity, schedule finding	0.5 mL, 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%
V72_41 Phase 3	11-17 yrs	Observer-blind, multicenter, randomized Safety and immunogenicity, lot consistency	0.5 mL, IM Schedule: 0, 1 mos	344 (342)	13.7 (11-17) yrs	55%
V72_75 Phase 3b	15-24 yrs	Open label, multicenter, controlled, extension study of V72P10 and V72_41 Immunogenicity, antibody persistence in adolescents and young adults	0.5 mL, IM Schedule: 0, 1; 0,2; 0,6 mos	531 (530) Follow-on subjects:275 Vaccine Naïve subjects: 255	19.7 (15-24) yrs	51%

[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] Groups I, II and III: Subjects Receiving a 2-or 3-Dose Primary Series Followed by a Booster Dose
[c] Group IV: Subjects Receiving a 2-Dose Catch-Up Series, Group IVa (children 2-5 years of age); Group IVb (children 6-10 years of age)
[d] Groups V and VI: Infants 3 months of age receiving a 2-dose primary series followed by a booster dose of BEXSERO with concomitant MenC-CRM or MenC-CRM alone
IM: intramuscular;
mos: months; yrs: years.

Immunogenicity Data

Immunogenicity of BEXSERO was evaluated in primary and extension studies. Most of the primary immunogenicity studies were conducted as randomized, multicenter clinical trials that enrolled infants, children, adolescents and adults (see Table 14). 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.

Table 15 - Summary of the Main Studies

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	• Demonstration of a sufficient immune response following a	• The fourth dose immune response was considered	Objectives were met. • For strains H44/76 and 5/99,

Study	Primary Immunogenicity Objectives	Prospectively Defined Criterion	Outcome
Phase 3	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 infants in Study V72P13.	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.	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 ≥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 in Infants aged 2 to 5 months

3+1 Infant Schedule

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 16. 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 17.

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 16). 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 16 - 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.
N= number of subjects with evaluable serum for analysis of that strain.

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.

2+1 Infant Schedule

The immunogenicity after two doses (at 3½ and 5 months of age) or three doses (at 2½, 3½ and 5 months of age) of BEXSERO followed by a booster has been evaluated in an additional phase 3 clinical study (Study V72_28). The percentages of seropositive subjects (i.e. achieving an hSBA of at least 1:4) ranged from 44% to 100% one month after the second dose and from 55% to 100% one month after the third dose, respectively for the two-dose schedule and the three-dose schedule. At one month following a booster administered 6 months after the last primary dose, the percentages of seropositive subjects ranged from 87% to 100% for the two-dose schedule, and from 83% to 100% for the three-dose schedule.

Antibody Persistence following 2+1 or 3+1 Infant Schedule

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 17).

Antibody persistence was evaluated in an extension study in children 3 to 4 years of age (Study V72_28E1). At 2 to 3 years after the completion of the vaccination course in Study V72_28, the antibody levels declined against all strains in both 2+1 and 3+1 schedules; the percentages of seropositive subjects (i.e. achieving an hSBA of at least 1:4) ranged from 35% to 91% or from 36% to 84%, respectively. In the same study the response to an additional dose administered 2 to 3 years after the booster was indicative of immunological memory as shown by a robust antibody response against all BEXSERO antigens, with seropositive rates ranging from 81% to 100% and from 70% to 99%, respectively.

Table 17 - 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
N= number of subjects with evaluable serum for analysis of that strain.

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, varicella, and meningococcal group C-CRM conjugate.

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.

A clinical study for concomitant use of BEXSERO with monovalent MenC-CRM conjugate vaccine showed that one month following 2 doses vaccination course and one month post-booster dose, the percentages of subjects achieving hSBA titers ≥8 against meningococcal serogroup C were comparable in both groups. Lower geometric mean titers (GMTs) were observed for meningococcal serotype-C (MenC-CRM vaccine) in the co-administration group than those seen in MenC-CRM administrated alone. Given that the titers in both groups were high, it is not likely that this difference will have a clinically significant impact.

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 months to 10 years

The immunogenicity after two doses in infants and children has been documented in three studies whose results are summarized in Table 18. Baseline GMTs were uniformly low against all three strains in the studies in infants 6 to 11 months of age and children 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 18.

Table 18 - 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 range).

[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.

hSBA = Serum Bactericidal Assay using human complement

GMT = Geometric Mean Titer.

N= number of subjects with evaluable serum for analysis of that strain.

In Study V72_28, participants received two doses of BEXSERO administered two months apart. The seroresponse rates and hSBA GMTs are shown in Table 19.

Table 19 - Serum bactericidal antibody responses at 1 month following the second dose of BEXSERO given to children 2-10 years of age following a 0, 2-month schedule

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

* % seropositive = the percentage of subjects who achieved an hSBA ≥ 1:4 (against reference strains for fHbp, NadA, PorA P1.4 antigens) and an hSBA ≥ 1:5 (against reference strain for NHBA antigen).
** GMT = geometric mean titre.
N= number of subjects with evaluable serum for analysis of that strain.

In the second study (V72_28E1), two doses of BEXSERO were administered one month apart in children 3 to 12 years of age. The percentages of seropositive children up to 10 years of age (i.e. achieving an hSBA of at least 1:4) across strains ranged from 46% to 95% at one month after the first dose and from 69% to 100% at one month after the second dose.

Immunogenicity in Adolescents aged 11 to 17 years

The immunogenicity data of two doses administered with an interval of one, two or six months in adolescents (V72P10, V72_41) are shown in Table 20. Baseline GMTs ranged from 2.61 to 4.11 in adolescents against fHbp, NadA and PorA P1.4 antigens. Baseline GMTs against NHBA antigen ranged from 30 to 32 in adolescents (V72P10).

Table 20 - Serum Bactericidal Antibody Responses in Adolescents One Month After Two Doses of BEXSERO Administered According to Different Two-Dose Schedules

Antigen		**V72_41 0, 1 months**	**V72P10 0, 1 months**	**V72P10 0, 2 months**	**V72P10 0, 6 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]
	hSBA GMT	117 (105-130)[b]	210 (193-229)[b]	234 (209-263)[b]	218 (157-302)[b]
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]
	hSBA GMT	179 (163-197)[b]	490 (455-528)[b]	734 (653-825)[b]	880 (675-1147)[b]
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]
	hSBA GMT	10 (8.77-12)[b]	92 (84-102)[b]	123 (107-142)[b]	140 (101-195)[b]
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 study 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.

N= number of subjects with evaluable serum for analysis of that strain.

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 to one month after the last dose of BEXSERO is summarized in Table 21.

Table 21 - Percentage of Adolescents With Seroresponse and at Least 4-Fold Rise[b] 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

[b] At least 4-fold rise = a post-vaccination hSBA ≥1:8 for subjects with pre-vaccination hSBA <1:2; a post-vaccination 4-fold rise for subjects with pre-vaccatination hSBA ≥1:2.

N= number of subjects with evaluable serum for analysis of that strain.

Immunogenicity in children and adolescents with complement deficiencies, and in individuals with splenic dysfunction or asplenia

In a phase 3b, open label clinical study (study V72_62), children and adolescents 2 to 17 years of age with complement deficiencies (n=40), with asplenia or splenic dysfunction (n=107), and age-matched healthy subjects (n=85) received two doses of BEXSERO two months apart. At 1 month following the 2-dose vaccination course, the percentages of subjects with hSBA ≥ 1:5 in individuals with complement deficiencies and asplenia or splenic dysfunction were 87% (95% CI: 72.6-95.7) and 97% (95% CI: 91.8-99.4) for antigen fHbp, 95% (95% CI: 82.3-99.4) and 100% (95% CI: 96.6-100) for antigen NadA, 68% (95% CI: 51.3-82.5) and 86% (95% CI: 77.7-91.9) for antigen PorA P1.4, 73% (95% CI: 55.9-86.2) and 94% (95% CI: 87.8-97.8) for antigen NHBA, respectively, indicating an immune response in these immunocompromised subjects. The percentages of healthy subjects with hSBA ≥ 1:5 were 98% (95% CI: 91.8-99.71) for antigen fHbp, 99% (95% CI: 93.5-99.97) for antigen NadA, 83% (95% CI: 73.6-90.6) for antigen PorA P1.4, and 99% (95% CI: 93.5-99.97) for antigen NHBA.

Adults

Data from study V72_75 were obtained in Canada and Australia after two doses of BEXSERO administered according to a 0-1 month schedule. Immunogenicity responses as given by percentages of subjects with hSBA ≥ 1:5 (seropositive threshold) and GMTs 1 month following 2 doses (0,1 month) of BEXSERO in subjects 18 to 24 years of age are presented in Table 22. The percentages of subjects with atleast a 4-fold rise at one month after the second dose compared to baseline ranged from 24% to 100% for fHbp, NadA and NHBA.

Table 22 - Serum Bactericidal Antibody Response[a] at 1 month after a 2-Dose Schedule in Canadian and Australian Adults (18 to 24 years of age)

Antigen	Study	V72_75[b]	
		Baseline	1 month after a 2-Dose Schedule (0,1 month)
fHbp	% seropositive (95% CI) N	6 (1.3-17.2) 48	98 (88.9-99.95) 48
	hSBA GMT (95% CI) N	1.17 (1.00-1.37) 48	45.09 (35 - 59) 48
NadA	% seropositive (95% CI) N	7 (1.4-18.7) 44	100 (92.3-100) 46
	hSBA GMT (95% CI) N	1.28 (1.00-1.66) 44	233.99 (177 - 309) 46
PorA P1.4	% seropositive (95% CI) N	0 (0-7.4) 48	77 (62.7-88) 48
	hSBA GMT (95% CI) N	1.00 (1.00-1.00) 48	12.39 (8.33 - 18) 48
NHBA	% seropositive (95% CI) N	54 (39.2-68.6) 48	88 (74.8-95.3) 48
	hSBA GMT (95% CI) N	8.97 (5.21-15) 48	30.38 (19-49) 48

Abbreviations: CI = confidence interval; hSBA = human serum bactericidal activity; GMT = geometric mean titers.
[a] Immunogenicity subset. % seropositive = the percentage of subjects who achieved an hSBA ≥ 1:5.
[b] N=145 follow on subjects and N=105 for naïve subjects
N= number of subjects with evaluable serum for analysis of that strain.

In study V72_75, antibody persistence data were obtained in Canada and Australia (V72_41), and in Chile (V72P10). At approximately 4 years, hSBA GMTs declined after the 2-dose primary series as adolescents in Canada and Australia. The percentages of subjects with hSBA ≥1:5 were 26% for fHbp, 84% for 5/99NadA, 9% for PorA P1.4, and 71% for NHBA. The response to a further dose after 4 years was indicative of immunological memory as 98% of subjects reached an hSBA ≥ 1:5 to fHbp, 100% to NadA, 92% to PorA P1.4, and 99% to NHBA, respectively. At approximately 7.5 years, hSBA GMTs declined after the 2-dose primary series as adolescent in Chile. The percentage of subjects with hSBA ≥ 1:4 was 44% for fHbp, 84% for NadA, 29% for PorA P1.4, and 78% for NHBA. The response to a further dose after 7.5 years was indicative of immunological memory as 100% of subjects reached an hSBA ≥1:4 to fHbp, 100% to NadA, 93% to PorA P1.4, and 98% to NHBA, respectively.

Limited immunogenicity data are available in subjects above 25 years of age in studies V72P4, V72P5 and V72P59. Ranges for the percentages of subjects with pre-existing hSBA ≥ 1:4/1:5 across studies in subjects above 25 years of age were: 0% to 39% for fHbp, 33% to 41% for NadA, 0% to 22% for PorA P.4. All subjects (100%) in V72_59 had hSBA ≥ 1:5 for NHBA. At 1 month after a 2-dose schedule of BEXSERO, majority of subjects achieved an hSBA ≥ 1:4/1:5

for each of the strains tested (range across studies: 100% for fHbp, 100% for NadA, 73% to 96% for PorA P1.4; and 100% for NHBA (study V72_59 only)).

DETAILED PHARMACOLOGY

Duration of Effect

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

TOXICOLOGY

Table 23 - 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

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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 25 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 mcg of recombinant *Neisseria meningitidis* group B NHBA fusion protein
50 mcg of recombinant *Neisseria meningitidis* group B NadA protein
50 mcg of recombinant *Neisseria meningitidis* group B fHbp fusion protein
25 mcg of Outer Membrane Vesicles *Neisseria meningitidis* group B strain NZ98/254

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

(mcg = micrograms)

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).
- your child was born prematurely (before or at 28 weeks of pregnancy), particularly with breathing difficulties. Stopping breathing or irregular breathing for a short time may be more common in the first three days following vaccination in these babies and they may need special monitoring.
- 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 individuals 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 limited 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, chickenpox, and meningococcus C. 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 to 5 months at the time of first dose
Your child should receive an initial course of two or three injections of the vaccine followed by an additional injection (booster).

The interval between vaccinations should be at least 2 months if two initial doses are given or at least 1 month if three initial doses are given. A booster will be given in the second year of life after an interval of at least 6 months from the last injection of the initial course.

Infants aged 6 months to 11 months of age at the time of first dose
Your child should receive two injections of the vaccine, given at least 2 months apart. A booster should be given 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.

Children aged 12 months to 23 months at the time of first dose
Your child should receive two injections of the vaccine, given at least 2 months apart. The need for further injections has not been established.

Children aged 2 years to 10 years at the time of first dose
Your child should receive two injections, given at least 1 month apart. The need for a third injection has not been established.

Adolescents and Adults aged 11 years through 25 years at the time of first dose
Individuals aged 11 through 25 years should receive two injections of the vaccine. 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, redness, swelling, or hardness of the skin at the injection site.

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

Infants and children (2 months 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.

Adolescents and Adults (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;
- collapse (sudden onset of muscle floppiness), less responsive than usual or lack of awareness, and paleness or bluish skin discoloration in young children;
- feeling faint or fainting;
- fever (adolescents from 11 years of age and adults); injection site reactions like extensive swelling of the vaccinated limb, blisters at or around the injection site and hard lump at the injection site (which may persist for more than one month).

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, GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4
1-800-387-7374

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