ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Bexsero suspension for injection in pre-filled syringe
Meningococcal group B Vaccine (rDNA, component, adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml) contains:

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.
White opalescent liquid suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bexsero is indicated for active immunisation of individuals from 2 months of age and older against invasive meningococcal disease caused by *Neisseria meningitidis* group B. The impact of invasive disease in different age groups as well as the variability of antigen epidemiology for group B strains in different geographical areas should be considered when vaccinating. See section 5.1 for information on protection against specific group B strains. The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Table 1. Summary of posology

Age Group	Primary Immunisation	Intervals between Primary Doses	Booster
Infants, 2 months to 5 months	Three doses each of 0.5 ml, with first dose given at 2 months of age [a]	Not less than 1 month	Yes, one dose between 12 and 15 months [b, c]
Unvaccinated infants, 6 months to 11 months	Two doses each of 0.5 ml	Not less than 2 months	Yes, one dose in the second year of life with an interval of at least 2 months between the primary series and booster dose [c]
Unvaccinated children, 12 months to 23 months	Two doses each of 0.5 ml	Not less than 2 months	Yes, one dose with an interval of 12 months to 23 months between the primary series and booster dose [c]
Children, 2 years to 10 years	Two doses each of 0.5 ml	Not less than 2 months	Need not established [d]
Adolescents (from 11 years of age) and adults*	Two doses each of 0.5 ml	Not less than 1 month	Need not established [d]

[a] The first dose should be given at 2 months of age. The safety and efficacy of Bexsero in infants less than 8 weeks of age has not yet been established. No data are available.

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

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

[d] See section 5.1.

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

Method of administration

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

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

The vaccine must not be injected intravenously, subcutaneously or intradermally and must not be mixed with other vaccines in the same syringe.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Do not inject intravascularly.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of 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 4.8). It is important that procedures are in place to avoid injury from fainting.

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

As with any vaccine, vaccination with Bexsero may not protect all vaccine recipients.
Bexsero is not expected to provide protection against all circulating meningococcal group B strains (see section 5.1).

As with many vaccines, healthcare professionals should be aware that a temperature elevation may occur following vaccination of infants and children (less than 2 years of age). Prophylactic administration of antipyretics at the time and closely after vaccination can reduce the incidence and intensity of post-vaccination febrile reactions. Antipyretic medication should be initiated according to local guidelines in infants and children (less than 2 years of age).

Individuals with impaired immune responsiveness, whether due to the use of immune-suppressive therapy, a genetic disorder, or other causes, may have reduced antibody response to active immunisation.
Immunogenicity data are available in individuals with complement deficiencies, asplenia, or splenic dysfunctions (see section 5.1).

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

The potential risk of apnoea and the need for respiratory monitoring for 48-72 hours should be considered when administering the primary immunisation series to very premature infants (born $\leq$ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Use with other vaccines

Bexsero can be given concomitantly with any of the following vaccine antigens, either as monovalent or as combination vaccines: diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, hepatitis B, heptavalent pneumococcal conjugate, measles, mumps, rubella, varicella, and meningococcal group C-CRM conjugate.

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

Due to an increased risk of fever, tenderness at the injection site, change in eating habits and irritability when Bexsero was co-administered with the above vaccines, separate vaccinations can be considered when possible. Prophylactic use of paracetamol reduces the incidence and severity of fever without affecting the immunogenicity of either Bexsero or routine vaccines. The effect of antipyretics other than paracetamol on the immune response has not been studied.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Insufficient clinical data on exposed pregnancies are available.

The potential risk for pregnant women is unknown. Nevertheless, vaccination should not be withheld when there is a clear risk of exposure to meningococcal infection.

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

Breast-feeding

Information on the safety of the vaccine to women and their children during breast-feeding is not available. The benefit-risk ratio must be examined before making the decision to immunise during breast-feeding.

No adverse reactions were seen in vaccinated maternal rabbits or in their offspring through day 29 of lactation. Bexsero was immunogenic in maternal animals vaccinated prior to lactation, and antibodies were detected in the offspring, but antibody levels in milk were not determined.

Fertility

There are no data on fertility in humans.

There were no effects on female fertility in animal studies.

4.7 Effects on ability to drive and use machines

Bexsero has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 “Undesirable effects” may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of Bexsero was evaluated in 14 studies including 10 randomised controlled clinical trials with 8776 subjects (from 2 months of age) who received at least one dose of Bexsero. Among Bexsero recipients, 5849 were infants and children (less than 2 years of age), 250 were children (2 to 10 years of age) and 2677 were adolescents and adults. Of the subjects who received primary infant series of Bexsero, 3285 received a booster dose in the second year of life. Data for a further 207 children exposed to Bexsero in a subsequent study have additionally been evaluated.

In infants and children (less than 2 years of age) the most common local and systemic adverse reactions observed in clinical trials were tenderness and erythema at the injection site, fever and irritability.

In clinical studies in infants vaccinated at 2, 4 and 6 months of age, fever (≥ 38°C) was reported by 69% to 79% of subjects when Bexsero was co-administered with routine vaccines (containing the following antigens: pneumococcal 7-valent conjugate, diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis and *Haemophilus influenzae* type b) compared with 44% to 59% of subjects receiving the routine vaccines alone. Higher rates of antipyretic use were also reported for infants vaccinated with Bexsero and routine vaccines. When Bexsero was given alone, the frequency of fever was similar to that associated with routine infant vaccines administered during clinical trials. When fever occurred, it generally followed a predictable pattern, with the majority resolving by the day after vaccination.

In adolescents and adults the most common local and systemic adverse reactions observed were pain at the injection site, malaise and headache.

No increase in the incidence or severity of the adverse reactions was seen with subsequent doses of the vaccination series.

Tabulated list of adverse reactions

Adverse reactions (following primary immunisation or booster dose) considered as being at least possibly related to vaccination have been categorised by frequency.

Frequencies are defined as follows:
Very common: (≥1/10)
Common: (≥1/100 to <1/10)
Uncommon: (≥1/1,000 to <1/100)
Rare: (≥1/10,000 to <1/1,000)
Very rare: (<1/10,000)
Not known: (cannot be estimated from the available data)

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

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

Infants and children (up to 10 years of age)

Immune system disorders
Not known: allergic reactions (including anaphylactic reactions)

Metabolism and nutrition disorders
Very common: eating disorders

Nervous system disorders
Very common: sleepiness, unusual crying, headache
Uncommon: seizures (including febrile seizures)
Not known: hypotonic-hyporesponsive episode

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

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

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

Musculoskeletal and connective tissue disorders
Very common: arthralgia

General disorders and administration site conditions
Very common: fever (≥38°C), injection site tenderness (including severe injection site tenderness defined as crying when injected limb is moved), injection site erythema, injection site swelling, injection site induration, irritability
Uncommon: fever (≥40°C)
Not known: 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)

Adolescents (from 11 years of age) and adults

Immune system disorders
Not known: allergic reactions (including anaphylactic reactions)

Nervous system disorders
Very common: headache
Not known: syncope or vasovagal responses to injection

Gastrointestinal disorders
Very common: nausea

Musculoskeletal and connective tissue disorders
Very common: myalgia, arthralgia

General disorders and administration site conditions
Very common: injection site pain (including severe injection site pain defined as unable to perform normal daily activity), injection site swelling, injection site induration, injection site erythema, malaise
Not known: fever, injection site reactions (including extensive swelling of the vaccinated limb, blisters at or around the injection site and injection site nodule which may persist for more than one month)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: meningococcal vaccines, ATC code: J07AH09

Mechanism of action

Immunisation with Bexsero is intended to stimulate the production of bactericidal antibodies that recognize the vaccine antigens NHBA, NadA, fHbp, and PorA P1.4 (the immunodominant antigen present in the OMV component) and are expected to be protective against Invasive Meningococcal Disease (IMD). As these antigens are variably expressed by different strains, meningococci that express them at sufficient levels are susceptible to killing by vaccine-elicited antibodies. The Meningococcal Antigen Typing System (MATS) was developed to relate antigen profiles of different strains of meningococcal group B bacteria to killing of the strains in the serum bactericidal assay with human complement (hSBA). A survey of approximately 1,000 different invasive meningococcal group B isolates collected during 2007-2008 in 5 European countries showed that, depending on the country of origin, between 73% and 87% of meningococcal group B isolates had an appropriate MATS antigen profile to be covered by the vaccine. Overall, 78% (95% confidence limits from 63-90%) of the approximately 1,000 strains were potentially susceptible to vaccine-induced antibodies.

Clinical efficacy

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

Immunogenicity

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

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

Immunogenicity in infants and children

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

Immunogenicity in infants 2 months to 6 months of age

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

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

Antigen		Study V72P13 2, 4, 6 months	Study V72P12 2, 3, 4 months	Study V72P16 2, 3, 4 months
fHbp	% seropositive* (95% CI)	N=1149 100% (99-100)	N=273 99% (97-100)	N=170 100% (98-100)
	hSBA GMT** (95% CI)	91 (87-95)	82 (75-91)	101 (90-113)
NadA	% seropositive (95% CI)	N=1152 100% (99-100)	N=275 100% (99-100)	N=165 99% (97-100)
	hSBA GMT (95% CI)	635 (606-665)	325 (292-362)	396 (348-450)
PorA P1.4	% seropositive (95% CI)	N=1152 84% (82-86)	N=274 81% (76-86)	N=171 78% (71-84)
	hSBA GMT (95% CI)	14 (13-15)	11 (9.14-12)	10 (8.59-12)
NHBA	% seropositive (95% CI)	N=100 84% (75-91)	N=112 37% (28-46)	N=35 43% (26-61)
	hSBA GMT (95% CI)	16 (13-21)	3.24 (2.49-4.21)	3.29 (1.85-5.83)

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

** GMT = geometric mean titer.

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

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

Antigen		2, 3, 4, 12 months	2, 4, 6, 12 months
fHbp	pre-booster* % seropositive** (95% CI) hSBA GMT*** (95% CI)	N=81 58% (47-69) 5.79 (4.54-7.39)	N=426 82% (78-85) 10 (9.55-12)
	1 month after booster % seropositive (95% CI) hSBA GMT (95% CI)	N=83 100% (96-100) 135 (108-170)	N=422 100% (99-100) 128 (118-139)
	12 months after booster % seropositive (95% CI) hSBA GMT (95% CI)	-	N=299 62% (56-67) 6.5 (5.63-7.5)
NadA	pre-booster % seropositive (95% CI) hSBA GMT (95% CI)	N=79 97% (91-100) 63 (49-83)	N=423 99% (97-100) 81 (74-89)
	1 month after booster % seropositive (95% CI) hSBA GMT (95% CI)	N=84 100% (96-100) 1558 (1262-1923)	N=421 100% (99-100) 1465 (1350-1590)
	12 months after booster % seropositive (95% CI) hSBA GMT (95% CI)	-	N=298 97% (95-99) 81 (71-94)
PorA P1.4	pre-booster % seropositive (95% CI) hSBA GMT (95% CI)	N=83 19% (11-29) 1.61 (1.32-1.96)	N=426 22% (18-26) 2.14 (1.94-2.36)
	1 month after booster % seropositive (95% CI) hSBA GMT (95% CI)	N=86 97% (90-99) 47 (36-62)	N=424 95% (93-97) 35 (31-39)
	12 months after booster % seropositive (95% CI) hSBA GMT (95% CI)	-	N=300 17% (13-22) 1.91 (1.7-2.15)
NHBA	pre-booster % seropositive (95% CI) hSBA GMT (95% CI)	N=69 25% (15-36) 2.36 (1.75-3.18)	N=100 61% (51-71) 8.4 (6.4-11)
	1 month after booster % seropositive (95% CI) hSBA GMT (95% CI)	N=67 76% (64-86) 12 (8.52-17)	N=100 98% (93-100) 42 (36-50)
	12 months after booster % seropositive (95% CI) hSBA GMT (95% CI)	-	N=291 36% (31-42%) 3.35 (2.88-3.9)

* pre-booster time point represents persistence of bactericidal antibody at 8 months after Bexsero vaccination at 2, 3 and 4 months of age and 6 months after Bexsero vaccination at 2, 4 and 6 months of age.

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

*** GMT = geometric mean titer.

A decline in antibody titers to PorA P1.4 and fHbp antigens (reaching 9%-10% and 12%-20% of subjects with an hSBA ≥ 1:5, respectively) has been observed in an additional study in children 4 years of age who received a full priming and booster schedule as infants. In the same study the response to a further dose was indicative of immunological memory as 81%-95% of subjects reached an hSBA ≥ 1:5 to PorA P1.4 and 97%-100% to fHbp antigens following further vaccination. The clinical significance of this observation and the need for additional booster doses to maintain longer term protective immunity has not been established.

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

The immunogenicity after two doses administered two months apart in children 6 months to 26 months of age has been documented in three studies whose results are summarised in Table 4. Against each of the vaccine antigens, seroresponse rates and hSBA GMTs were high and similar after the two-dose series in infants 6-8 months of age and children, 13-15 and 24-26 months of age. Data on antibody persistence one year after the two doses at 13 and 15 months of age are also summarised in Table 4.

Table 4. Serum bactericidal antibody responses following Bexsero vaccination at 6 and 8 months of age, 13 and 15 months of age, or 24 and 26 months of age and persistence of bactericidal antibody one year after the two doses at 13 and 15 months of age

Antigen		Age range		
		6 to 11 months of age	**12 to 23 months of age**	**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* (95% CI) hSBA GMT** (95% CI)	N=23 100% (85-100) 250 (173-361)	N=163 100% (98-100) 271 (237-310)	N=105 100% (97-100) 220 (186-261)
	12 months after 2nd dose % seropositive (95% CI) hSBA GMT (95% CI)	-	N=68 74% (61-83) 14 (9.4-20)	-
NadA	1 month after 2nd dose % seropositive (95% CI) hSBA GMT (95% CI)	N=23 100% (85-100) 534 (395-721)	N=164 100% (98-100) 599 (520-690)	N=103 99% (95-100) 455 (372-556)
	12 months after 2nd dose % seropositive (95% CI) hSBA GMT (95% CI)	-	N=68 97% (90-100) 70 (47-104)	-
PorA P1.4	1 month after 2nd dose % seropositive (95% CI) hSBA GMT (95% CI)	N=22 95% (77-100) 27 (21-36)	N=164 100% (98-100) 43 (38-49)	N=108 98% (93-100) 27 (23-32)
	12 months after 2nd dose % seropositive (95% CI) hSBA GMT (95% CI)	-	N=68 18% (9-29) 1.65 (1.2-2.28)	-
NHBA	1 month after 2nd dose % seropositive (95% CI) hSBA GMT (95% CI)	-	N=46 63% (48-77) 11 (7.07-16)	N=100 97% (91-99) 38 (32-45)
	12 months after 2nd dose % seropositive (95% CI) hSBA GMT (95% CI)	-	N=65 38% (27-51) 3.7 (2.15-6.35)	-

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

** GMT = geometric mean titer.

In an additional group of 67 children evaluated after vaccination with Bexsero at 40 to 44 months of age in two extension studies (N=36 and N=29-31, respectively), an increase in hSBA titers for the four reference antigens was observed. Percentages of seropositive subjects were 100% for fHbp and NadA; 94% and 90% for PorA P1.4; 89% and 72% for NHBA.

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

Adolescents received two doses of Bexsero with one, two or six month intervals between doses; these data are summarised in Tables 5 and 6.

In studies with adults, data were obtained after two doses of Bexsero with a one month or two month interval between doses (see Table 7).

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

Table 5. Serum bactericidal antibody responses in adolescents one month after two doses of Bexsero administered according to different two-dose schedules and persistence of bactericidal antibody 18 to 23 months after the second dose

Antigen		0, 1 months	0, 2 months	0, 6 months
fHbp	1 month after 2nd dose	N=638	N=319	N=86
	% seropositive* (95% CI)	100% (99-100)	100% (99-100)	100% (99-100)
	hSBA GMT** (95% CI)	210 (193-229)	234 (209-263)	218 (157-302)
	18-23 months after 2nd dose	N=102	N=106	N=49
	% seropositive (95% CI)	82% (74-89)	81% (72-88)	84% (70-93)
	hSBA GMT (95% CI)	29 (20-42)	34 (24-49)	27 (16-45)
NadA	1 month after 2nd dose	N=639	N=320	N=86
	% seropositive (95% CI)	100% (99-100)	99% (98-100)	99% (94-100)
	hSBA GMT (95% CI)	490 (455-528)	734 (653-825)	880 (675-1147)
	18-23 months after 2nd dose	N=102	N=106	N=49
	% seropositive (95% CI)	93% (86-97)	95% (89-98)	94% (83-99)
	hSBA GMT (95% CI)	40 (30-54)	43 (33-58)	65 (43-98)
PorA P1.4	1 month after 2nd dose	N=639	N=319	N=86
	% seropositive (95% CI)	100% (99-100)	100% (99-100)	100% (96-100)
	hSBA GMT (95% CI)	92 (84-102)	123 (107-142)	140 (101-195)
	18-23 months after 2nd dose	N=102	N=106	N=49
	% seropositive (95% CI)	75% (65-83)	75% (66-83)	86% (73-94)
	hSBA GMT (95% CI)	17 (12-24)	19 (14-27)	27 (17-43)
NHBA	1 month after 2nd dose	N=46	N=46	-
	% seropositive (95% CI)	100% (92-100)	100% (92-100)	-
	hSBA GMT (95% CI)	99 (76-129)	107 (82-140)	-

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

** GMT = geometric mean titer.

In the adolescent study, bactericidal responses following two doses of Bexsero were stratified by baseline hSBA less than 1:4 or equal to or greater than 1:4. Seroresponse rates and percentages of subjects with at least a 4-fold increase in hSBA titer from baseline to one month after the second dose of Bexsero are summarised in Table 6. Following Bexsero vaccination, a high percentage of subjects were seropositive and achieved 4-fold increases in hSBA titers independent of pre-vaccination status.

Table 6. Percentage of adolescents with seroresponse and at least 4-fold rise in bactericidal titers one month after two doses of Bexsero administered according to different two-dose schedules - stratified by pre-vaccination titers

Antigen			0, 1 months	0, 2 months	0, 6 months
fHbp	% seropositive* after 2nd dose (95% CI)	pre-vaccination titer <1:4	N=369 100% (98-100)	N=179 100% (98-100)	N=55 100% (94-100)
		pre-vaccination titer ≥1:4	N=269 100% (99-100)	N=140 100% (97-100)	N=31 100% (89-100)
	% 4-fold increase after 2nd dose (95% CI)	pre-vaccination titer <1:4	N=369 100% (98-100)	N=179 100% (98-100)	N=55 100% (94-100)
		pre-vaccination titer ≥1:4	N=268 90% (86-93)	N=140 86% (80-92)	N=31 90% (74-98)
NadA	% seropositive after 2nd dose (95% CI)	pre-vaccination titer <1:4	N=427 100% (99-100)	N=211 99% (97-100)	N=64 98% (92-100)
		pre-vaccination titer ≥1:4	N=212 100% (98-100)	N=109 100% (97-100)	N=22 100% (85-100)
	% 4-fold increase after 2nd dose (95% CI)	pre-vaccination titer <1:4	N=426 99% (98-100)	N=211 99% (97-100)	N=64 98% (92-100)
		pre-vaccination titer ≥1:4	N=212 96% (93-98)	N=109 95% (90-98)	N=22 95% (77-100)
PorA P1.4	% seropositive after 2nd dose (95% CI)	pre-vaccination titer <1:4	N=427 100% (98-100)	N=208 100% (98-100)	N=64 100% (94-100)
		pre-vaccination titer ≥1:4	N=212 100% (98-100)	N=111 100% (97-100)	N=22 100% (85-100)
	% 4-fold increase after 2nd dose (95% CI)	pre-vaccination titer <1:4	N=426 99% (98-100)	N=208 100% (98-100)	N=64 100% (94-100)
		pre-vaccination titer ≥1:4	N=211 81% (75-86)	N=111 77% (68-84)	N=22 82% (60-95)
NHBA	% seropositive after 2nd dose (95% CI)	pre-vaccination titer <1:4	N=2 100% (16-100)	N=9 100% (66-100)	-
		pre-vaccination titer ≥1:4	N=44 100% (92-100)	N=37 100% (91-100)	-
	% 4-fold increase after 2nd dose (95% CI)	pre-vaccination titer <1:4	N=2 100% (16-100)	N=9 89% (52-100)	-
		pre-vaccination titer ≥1:4	N=44 30% (17-45)	N=37 19% (8-35)	-

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

Table 7. Serum bactericidal antibody responses in adults after two doses of Bexsero administered according to different two-dose schedules

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

* % seropositive = the percentage of subjects who achieved an hSBA ≥ 1:4.
** GMT = geometric mean titer.
Serum bactericidal response to NHBA antigen has not been evaluated.

Immunogenicity in special populations

Children and adolescents with complement deficiencies, asplenia, or splenic dysfunction

In a phase 3 clinical study, children and adolescents 2 through 17 years of age with complement deficiencies (40), with asplenia or splenic dysfunction (107), and age-matched healthy subjects (85) received two doses of Bexsero two months apart. At 1 month following the 2-dose vaccination course, the percentages of subjects with hSBA ≥1:5 in individuals with complement deficiencies and asplenia or splenic dysfunction were 87% and 97% for antigen fHbp, 95% and 100% for antigen NadA, 68% and 86% for antigen PorA P1.4, 73% and 94% for antigen NHBA, respectively, indicating an immune response in these immunocompromised subjects. The percentages of healthy subjects with hSBA ≥1:5 were 98% for antigen fHbp, 99% for antigen NadA, 83% for antigen PorA P1.4, and 99% for antigen NHBA.

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

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Histidine
Sucrose
Water for injections

For adsorbent see section 2.

6.2 Incompatibilities

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

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

0.5 ml suspension in a pre-filled syringe (Type I glass) with a plunger stopper (Type I bromobutyl rubber) and with a protective tip cap (Type I or Type II rubber) with or without needles.

Pack sizes of 1 or 10 syringes. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

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

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

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

7. MARKETING AUTHORISATION HOLDER

GSK Vaccines S.r.l.,
Via Fiorentina 1,
53100 Siena,
Italy

8. MARKETING AUTHORISTION NUMBER(S)

EU/1/12/812/001
EU/1/12/812/002
EU/1/12/812/003
EU/1/12/812/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 January 2013
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

DD/MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substances (NHBA, NadA, fHbp):

Sandoz GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

Name and address of the manufacturers of the biological active substance (OMV):

GSK Vaccines S.r.l.
Bellaria-Rosia
IT-53018 Sovicille-Siena
Italy

GSK Vaccines S.r.l.
Via Fiorentina, 1
IT-53100 Siena
Italy

Name and address of the manufacturer responsible for batch release:

GSK Vaccines S.r.l.
Bellaria-Rosia
IT-53018 Sovicille-Siena
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Bexsero suspension for injection in pre-filled syringe
Meningococcal Group B Vaccine (rDNA, component, adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

0.5 ml dose contains:

Recombinant *Neisseria meningitidis* group B NHBA fusion/NadA/fHbp fusion proteins	50/50/50 micrograms
Outer membrane vesicles (OMV) from *Neisseria meningitidis* group B strain NZ98/254 measured as amount of total protein containing the PorA P1.4	25 micrograms

Adsorbed on aluminium hydroxide (0.5 mg Al^{3+}).

3. LIST OF EXCIPIENTS

Excipients: sodium chloride, histidine, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection (0.5 ml)
1 pre-filled syringe containing 0.5 ml suspension with needles
1 pre-filled syringe containing 0.5 ml suspension without needle

10 pre-filled syringes each containing 0.5 ml suspension with needles
10 pre-filled syringes each containing 0.5 ml suspension without needle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use only.

Shake well before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GSK Vaccines S.r.l.,
Via Fiorentina 1,
53100 Siena,
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/812/001
EU/1/12/812/002
EU/1/12/812/003
EU/1/12/812/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Bexsero suspension for injection
Meningococcal B vaccine
IM use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 ml)

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: information for the user

Bexsero suspension for injection in pre-filled syringe
Meningococcal group B Vaccine (rDNA, component, adsorbed)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you or your child receive this medicine because it contains important information for you or your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This vaccine has been prescribed for you or your child only.
- If you get any side effects talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Bexsero is and what it is used for
2. What you need to know before you or your child receive Bexsero
3. How to use Bexsero
4. Possible side effects
5. How to store Bexsero
6. Contents of the pack and other information

1. What BEXSERO is and what it is used for

Bexsero is a Meningococcal group B Vaccine.

Bexsero contains four different components from the surface of the bacteria *Neisseria meningitidis* group B.

Bexsero is given to individuals from 2 months of age and older to help protect against disease caused by the *Neisseria meningitidis* group B bacteria. These bacteria can cause serious, and sometimes life-threatening, infections such as meningitis (inflammation of the covering of the brain and spinal cord) and sepsis (blood poisoning).

The vaccine works by specifically stimulating the body's natural defense system of the vaccinated person. This results in protection against the disease.

2. What you need to know before you or your child receive BEXSERO

Do NOT use Bexsero:

- If you or your child are allergic to the active substances or any of the other ingredients of this vaccine (listed in section 6).

Warnings and precautions

Talk to your doctor or nurse before you or your child receive Bexsero, 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 or nurse first.

- haemophilia or any other problem that may stop your blood from clotting properly, such as treatment with blood thinners (anticoagulants). Talk to your doctor or nurse first.
- if your child was born prematurely (before or at 28 weeks of pregnancy), particularly if they had breathing difficulties, please tell your doctor. 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.
- 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 or 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 or nurse if you know that you or your child is allergic to latex. The tip cap of the syringe may contain natural rubber latex. The risk for developing an allergic reaction is very small, but your doctor or nurse needs to be aware of your allergy when deciding if you or your child should receive Bexsero.

There are no data on the use of Bexsero in adults above 50 years of age. 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 defence 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.

Other medicines and Bexsero

Tell your doctor or 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 components: diphtheria, tetanus, whooping cough (pertussis), *Haemophilus influenzae* type b, polio, hepatitis B, pneumococcus, measles, mumps, rubella, chickenpox, and meningococcus C. Talk to your doctor or nurse for further information.

When given at the same time with other vaccines Bexsero must be given at separate injection sites.

Your doctor or 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.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before Bexsero is given. Your doctor may still recommend that you receive Bexsero if you are at risk of exposure to meningococcal infection.

Driving and using machines

Bexsero has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4 "Possible side effects" may temporarily affect the ability to drive or use machines.

Bexsero contains sodium chloride

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

3. How to use BEXSERO

Bexsero (0.5 ml) will be given to you or your child by a doctor or nurse. It will be injected into a muscle, usually the thigh for infants or the upper arm for children, adolescents and adults.

It is important to follow the instructions from the doctor or nurse so that you or your child completes the course of injections.

Infants 2 months to 5 months of age

Your child should receive an initial course of three injections of the vaccine followed by a fourth injection (booster).
- The first injection should be given at 2 months of age.
- The interval between each injection should be at least 1 month.
- A fourth injection (booster) will be given between 12 months and 15 months of age. In case of delay, the booster should not be given later than 24 months.

Infants 6 months to 11 months of age

Unvaccinated infants 6 months to 11 months of age should receive two injections followed by a third injection (booster).
- The interval between the injections should be at least 2 months.
- A third injection (booster) will be given in the second year of life after an interval of at least 2 months from the second injection.

Children 12 months to 23 months of age

Children 12 months to 23 months of age should receive two injections followed by a third injection (booster).
- The interval between each injection should be at least 2 months
- A third injection (booster) will be given after an interval of 12 to 23 months from the second injection.

Children 2 years to 10 years of age

Children 2 years to 10 years of age should receive two injections.
- The interval between each injection should be at least 2 months.

Adolescents (from 11 years of age) and adults

Adolescents (from 11 years of age) and adults should receive two injections.
- The interval between each injection should be at least 1 month.

Adults above 50 years of age

There are no data in adults above 50 years of age. Ask your doctor for advice whether it is beneficial for you to receive Bexsero.

If you have any further questions on Bexsero, ask your doctor or nurse.

4. Possible side effects

Like all vaccines, this vaccine can cause side effects, although not everybody gets them.

When Bexsero is given to you or your child, the very common side effects (may affect more than 1 in 10 people) that you or your child may get (reported in all age groups) are:

- pain/tenderness at the injection site, redness of the skin at the injection site, swelling of the skin at the injection site, hardness of the skin at the injection site.

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

Infants and children (up to 10 years of age)

Very common (these may affect more than 1 in 10 people)
- fever (≥38ºC)
- loss of appetite
- tenderness or discomfort at the injection site (including severe injection site tenderness resulting in crying when injected limb is moved)
- painful joints
- skin rash (children aged 12 to 23 months) (uncommon after booster)
- sleepiness
- feeling irritable
- unusual crying
- vomiting
- diarrhea
- headache

Common (these may affect up to 1 in 10 people)
- skin rash (infants and children 2 to 10 years of age)

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

Adolescents (from 11 years of age) and adults

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).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store BEXSERO

Keep this vaccine out of the sight and reach of children.

Do not use this vaccine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C). Do not freeze.
Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your doctor or nurse how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Bexsero contains

One dose (0.5 ml) contains:

Active substances:

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

1 produced in *E. coli* cells by recombinant DNA technology
2 adsorbed on aluminium hydroxide (0.5 mg Al^{3+})
3 NHBA (Neisseria Heparin Binding Antigen), NadA (Neisserial adhesin A), fHbp (factor H binding protein)

Other ingredients:
Sodium chloride, histidine, sucrose and water for injections (see section 2 for further information on sodium and latex).

What Bexsero looks like and contents of the pack

Bexsero is a suspension for injection in pre-filled syringe (Type I glass) with a plunger stopper (Type I bromobutyl rubber) and with a protective tip cap (Type I or Type II rubber) with or without needles.

Pack sizes of 1 or 10 syringes.
The suspension is white opalescent liquid.

Not all pack sizes may be marketed.

Marketing Authorisation Holder:

GSK Vaccines S.r.l.

Via Fiorentina 1
53100 Siena
Italy.

Manufacturer:

GSK Vaccines S.r.l.
Bellaria-Rosia
53018 Sovicille (Siena)
Italy.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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customercontactuk@gsk.com

This leaflet was last revised in *MM/YYYY}*

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

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

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

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

Do not freeze.
Bexsero must not be mixed with other vaccines in the same syringe.
Should concomitant administration of other vaccines be necessary, vaccines must be administered at separate injection sites.

Care must be taken to ensure that the vaccine is injected intramuscularly only.

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