1. NAME OF THE MEDICINAL PRODUCT

Meningococcal Group A, C, W-135 and Y conjugate vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml of the reconstituted vaccine) contains:

(Originally contained in the powder)

• Meningococcal group A oligosaccharide	10 micrograms
Conjugated to *Corynebacterium diphtheriae* CRM_{197} protein	16.7 to 33.3 micrograms

(Originally contained in the solution)

• Meningococcal group C oligosaccharide	5 micrograms
Conjugated to *Corynebacterium diphtheriae* CRM_{197} protein	7.1 to 12.5 micrograms
• Meningococcal group W-135 oligosaccharide	5 micrograms
Conjugated to *Corynebacterium diphtheriae* CRM_{197} protein	3.3 to 8.3 micrograms
• Meningococcal group Y oligosaccharide	5 micrograms
Conjugated to *Corynebacterium diphtheriae* CRM_{197} protein	5.6 to 10.0 micrograms

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solution for solution for injection.
The powder is a white to off- white cake.
The solution is a colourless clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Menveo is indicated for active immunization of children (from 2 months of age), adolescents and adults at risk of exposure to *Neisseria meningitidis* groups A, C, W-135 and Y, to prevent invasive disease.
The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

- Vaccine schedule for children from 2 to 23 months of age

In infants initiating vaccination from 2 to 6 months of age, three doses of Menveo, each of 0.5 ml, should be given with an interval of at least 2 months; the fourth dose should be administered during the second year of life (at 12-16 months).

In unvaccinated children from 7 to 23 months of age, Menveo should be administered as two doses, each as a single dose (0.5 ml), with the second dose administered in the second year of life and at least two months after the first dose.

- Vaccine schedule for children 2 to 10 years of age

Menveo is to be administered as single dose (0.5 ml).

- Vaccine schedule for adolescents and adults (from 11 years of age)

Menveo is to be administered as single dose (0.5 ml).

Booster
The need for, and timing of, a booster dose of Menveo has not yet been determined.

Elderly

There are limited data in individuals aged 56-65 and there are no data in individuals aged >65 years.

Method of administration

Each Menveo dose is to be administered as a single 0.5ml intramuscular injection, preferably into the anterolateral aspect of the thigh in infants or into the deltoid muscle (upper arm) in children, adolescents and adults.
It must not be administered intravascularly, subcutaneously or intradermally.

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

For instructions on preparation and reconstitution of the product, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients of the vaccine, including diphtheria toxoid (CRM_{197}), or a life-threatening reaction after previous administration of a vaccine containing similar components (see section 4.4).

4.4 Special warnings and precautions for use

Before the injection of any vaccine, the person responsible for administration must take all precautions known for the prevention of allergic or any other reactions including thorough medical history and current health status. As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in case of a rare anaphylactic event following 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 Undesirable effects). It is important that procedures are in place to avoid injury from fainting.

Menveo should under no circumstances be administered intravascularly.

Menveo will not protect against infections caused by any other serogroups of *N. meningitidis*
not present in the vaccine.As with any vaccine, a protective immune response may not be elicited in all vaccinees (see section 5.1).

There are no data on the applicability of the vaccine for post-exposure prophylaxis.

In immunocompromised individuals, vaccination may not result in an appropriate protective antibody response. While Human Immunodeficiency Virus (HIV) infection is not a contraindication, Menveo has not been specifically evaluated in immunocompromised people. Individuals with complement deficiencies and individuals with functional or anatomical asplenia may not mount an immune response to meningococcal group A, C, W-135 and Y conjugate vaccines.

Menveo has not been evaluated in persons with thrombocytopenia, bleeding disorders or that are receiving anticoagulant therapy, because of the risk of haematoma. The risk-benefit ratio for persons at risk of haematoma following intramuscular injection must be evaluated by health care professionals.

As with other vaccines, Menveo should be postponed in individuals suffering from an acute severe febrile illness. The presence of a minor infection is not a contraindication.

Guillain-Barré syndrome (GBS) has been reported in temporal relationship following administration of another meningococcal quadrivalent polysaccharide conjugate vaccine. A recent large multi-site retrospective cohort and nested case control study, found no evidence of increased GBS risk associated with the use of that vaccine. The decision to administer Menveo to subjects with a known history of Guillain-Barré Syndrome should take into account the potential benefits and risks.

4.5 Interaction with other medicinal products and other forms of interaction

Do not mix Menveo or any of its components with any other vaccine or diluent in the same syringe or vial.

In two clinical trials of infants initiating vaccination at 2 months of age, Menveo was given concomitantly at 2, 4 and 6 months with routine infant vaccines: diphtheria toxoid, acellular pertussis, tetanus toxoid, inactivated polio types 1, 2 and 3, hepatitis B, *Haemophilus influenzae* type b (Hib) antigens; pentavalent rotavirus, and 7-valent pneumococcal conjugate vaccine. For dose 4 given at 12 months of age, Menveo was given concomitantly with the following vaccines: 7-valent pneumococcal conjugate, MMRV or MMR+V, and inactivated hepatitis A. In a clinical trial of older infants (≥ 7 months of age) and toddlers, Menveo was administered concomitantly with MMRV or MMR+V vaccine(s) at 12 months of age. No immune interference was observed for the concomitantly administered vaccines with exception of pneumococcal vaccine serotype 6B and 23F post-dose 3; no immune interference was observed post-dose 4 for any pneumococcal vaccine serotypes.

For children 2 years through 10 years of age, no data are available to evaluate safety and immunogenicity of other childhood vaccines when administered concomitantly with Menveo. In the adolescents (11 to 18 years of age), Menveo can be given concomitantly with tetanus, reduced diphtheria and acellular pertussis vaccine (Tdap) and human papillomavirus quadrivalent (Types 6, 11, 16 and 18) recombinant vaccine (HPV).

In this age group, Menveo has been evaluated in two co-administration studies with either Tdap alone or Tdap and HPV. There was no evidence of an increased rate of reactogenicity or change in the safety profile of the vaccines in either study. Antibody responses to Menveo and the diphtheria, tetanus, pertussis or HPV vaccine components were not negatively affected by co-administration. The sequential administration of Menveo one month after Tdap resulted in lower immune response for serogroup W-135 as measured by percentage of subjects with seroresponse. Since at least 95% of subjects reached hSBA≥1:8 for serogroup W-135 post-vaccination, the clinical relevance of this observation is unknown.

In adults Menveo can be administered concomitantly with other vaccines: combined hepatitis A/B, yellow fever, typhoid fever (Vi polysaccharide), Japanese encephalitis and rabies. The concomitant administration of Menveo with combined hepatitis A/B vaccine, or typhoid fever and yellow fever vaccines, or with Japanese encephalitis and rabies virus vaccines was evaluated in a clinical trial in adults. No clinically relevant interference was shown in the antibody response to the hepatitis A and B, typhoid Vi polysaccharide, yellow fever, Japanese encephalitis and rabies virus antigens after the completion of the vaccination series. Antibody responses to Menveo were not negatively affected by co-administration. No change in the safety profile of the vaccines was observed.

Concomitant administration of Menveo and other vaccines than those listed above has not been studied. It is advised that Menveo should not be administered at the same time as other vaccines in particular live vaccines, unless absolutely necessary. Concomitant vaccines should always be administered at separate injection sites and preferably contralateral.

If a vaccine recipient is undergoing immunosuppressant treatment, the immunological response may be diminished.

4.6 Pregnancy and lactation

Pregnancy
Insufficient clinical data on exposed pregnancies are available.

In non-clinical studies, Menveo had no direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Considering the severity of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W-135 and Y, pregnancy should not preclude vaccination when the risk of exposure is clearly defined.

Breast-feeding
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Menveo is administered to a nursing woman. No studies have been conducted to assess the impact of Menveo on milk production, its presence in breast milk or its effects on the breast-fed child.

Fertility
The effect of Menveo on embryo-fetal and post-natal development was evaluated in pregnant rabbits. Animals were administered Menveo 3 times prior to gestation, during the period of organogenesis (gestation day 7) and later in pregnancy (gestation day 20), 0.5 mL/rabbit/occasion (approximately 20-fold excess relative to the projected human dose on a body weight basis) by intramuscular injections. There were no adverse effects

attributable to the vaccine on mating, female fertility, pregnancy, or embryo-fetal development. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in this study.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Dizziness has been very rarely reported following vaccination. This may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Adverse Reactions from Clinical Trials

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

Children 2 to 23 months of age

The safety of Menveo administered as 4-dose schedule was evaluated in three randomized, controlled multicenter clinical studies in which 8735 infants 2 months of age at enrolment received Menveo concomitantly with routine paediatric vaccines (see section 8). A total of 2864 infants received the routine paediatric vaccines alone. There was no significant increase in the rates of solicited systemic or local reactions observed in recipients of routine paediatric vaccines when concomitantly vaccinated with Menveo.

In infants initiating vaccination at 2 months of age and receiving the four-dose series, common solicited adverse reactions (> 10%) were tenderness (24-41%) and erythema at injection site (11-15%), irritability (42-57%), sleepiness (29-50%), persistent crying (21-41%), change in eating habits (17-23%), vomiting (5-11%) and diarrhea (8-16%). The rates of solicited adverse reactions reported for subjects aged 2 months and above receiving Menveo with routine vaccines at 2, 4, 6 and 12 months of age were comparable to rates among subjects who only received routine vaccines.

The safety of Menveo with 2-dose schedule was assessed in 1985 children immunized between 6 and 23 months of age was evaluated in three randomized studies that addressed the safety of Menveo administered concomitantly with routine paediatric vaccines. Common solicited adverse reactions (≥10%) among children initiating vaccination at 7 months through 23 months of age and receiving the two-dose series were tenderness (10-16%) and erythema at injection site (12-15%), irritability (27-40%), sleepiness (17-29%), persistent crying (12-21%), change in eating habits (12-20%) and diarrhea (10-16%).
In two studies, the safety of one dose of Menveo when given concomitantly with

routine paediatric vaccines in the second year of life was evaluated in 345 subjects.

Most of the common adverse reactions occurred within the first several days after vaccination and few were severe. The observed adverse reactions were:

Metabolism and nutrition disorders:
Very common: eating disorder

Nervous system disorders:
Very common: persistent crying, sleepiness

Gastrointestinal disorders:
Very common: diarrhea, vomiting

Skin and subcutaneous tissue disorders:
Common: rash

General disorders and administration site conditions:
Very common: irritability, injection site tenderness, injection site erythema (≤50 mm), injection site induration (≤50 mm)
Common: severe injection site tenderness, fever
Uncommon: injection site erythema (>50 mm), injection site induration (>50 mm)

Children 2 to 10 years of age

The safety of Menveo in children 2 to 10 years of age was evaluated in 4 clinical trials in which 3181 subjects received Menveo. Local and systemic reactogenicity rates as well as rates of other adverse events were generally similar between Menveo and comparator vaccines (quadrivalent diphtheria toxoid conjugate meningococcal vaccine (ACWY-D) or quadrivalent meningococcal polysaccharide vaccine (ACWY-PS)) recipients.

The most common adverse reactions during the clinical trials generally persisted for one to two days and were not severe. These adverse reactions were:

Metabolism and nutrition disorders:
Common: eating disorder

Nervous system disorders:
Very common: sleepiness, headache

Gastrointestinal disorders:
Common: nausea, vomiting, diarrhea

Skin and subcutaneous tissue disorders:
Common: rash

Musculoskeletal and connective tissue disorders:
Common: myalgia, arthralgia

General disorders and administration site conditions:

Very common: irritability, malaise, injection site pain, injection site erythema (≤ 50 mm), injection site induration (≤ 50 mm)
Common: injection site erythema (>50mm), injection site induration (>50mm), chills, fever ≥38^{o}C
Uncommon: injection site pruritus

Individuals 11 to 65 years of age

In adolescents and adults, the safety of Menveo was evaluated in five randomized controlled clinical trials including 6401 participants (from 11-65 years) who received Menveo. Among Menveo recipients, 58.9%, 16.4%, 21.3% and 3.4% were in the 11-18 year, 19-34 year, 35-55 year and 56-65 year age groups, respectively. The two primary safety studies were randomized, active-controlled trials that enrolled participants aged 11 to 55 years (N=2663) and 19 to 55 years (N=1606), respectively.

The incidence and severity of any, local, systemic, and other reactions were generally similar in the Menveo groups across all studies and within the adolescent and adult age groups. The reactogenicity profile and rates of adverse events among subjects aged 56-65 years who received Menveo (N=216), were similar to that observed in Menveo recipients subjects aged 11-55 years.

The most common local and systemic adverse reactions observed in clinical trials were pain at the injection site and headache.

Adverse reactions reported in three pivotal and two supportive clinical trials are listed here below per system organ class. The most common side effects reported during clinical trials usually lasted only one to two days and were not usually severe.

Nervous system disorders:
Very common: headache
Uncommon: dizziness

Gastrointestinal disorders:
Very common: nausea

Skin and subcutaneous tissue disorders:
Common: rash

Musculoskeletal and connective tissue disorders
Very common: myalgia
Common: arthralgia

General disorders and administration site conditions:
Very common: injection site pain, injection site erythema (≤50 mm), injection site induration (≤50 mm), malaise
Common: injection site erythema (>50 mm), injection site induration (>50 mm), fever ≥38°C, chills
Uncommon: injection site pruritus

In the adolescent age group, the safety and tolerability of the vaccine was favourable relative to Tdap and did not substantially change with concomitant or sequential

administration of other vaccines.

Serious Adverse Events in All Safety Studies

Serious adverse events in subjects receiving a four-dose series of Menveo at 2, 4, 6 and 12 months were evaluated in three randomized multicenter clinical studies 1-3. In the two controlled studies 2, 3, the proportions of infants randomized to receive the four-dose Menveo series concomitantly with routine vaccinations and infants who received routine vaccinations alone that reported serious adverse events during different study periods were, respectively: a) 2.7% and 2.2%, during the infant series; b) 2.5% and 2.5%, between the infant series and the toddler dose; c) 0.3% and 0.3%, in the one month following the toddler dose; and d) 1.6% and 2.2%, during the 6 months follow up period after the last dose. In the third study 1, which was controlled up to the toddler dose, the proportions of infants randomized to dosing regimens that included receiving four doses of Menveo concomitantly with routine vaccinations at 2, 4, 6, and 12 months and infants who received routine vaccinations alone that reported serious adverse events during different study periods were, respectively: a) 3.5% and 3.6%, during the infant series; and b) 2.8% and 3.3%, between the infant series and the toddler dose; and c) 0.5% and 0.7%, in the one month following the toddler dose. In the same study, 1.9% of infants randomized to receive the four-dose Menveo series concomitantly with routine vaccinations reported serious adverse events during the 6 month follow up period after the toddler dose. The most common serious adverse events reported in these three studies were wheezing, pneumonia, gastroenteritis and convulsions, and most occurred at highest frequency after the infant series.

In a study of older infants 5 randomized to receive the two-dose Menveo series concomitantly with MMRV at 12 months of age, the rates of serious adverse events during the study, including the 6-month follow-up period after the last dose, were 3.6% and 3.8%, for the Menveo with MMRV and Menveo-only groups, respectively. Infants receiving MMRV alone, who had a shorter period of study participation as they were enrolled at 12 months of age, had a lower rate of serious adverse events (1.5%). Among 1597 study subjects, included in the safety population, the most commonly reported serious adverse events in all study arms combined were dehydration (0.4%) and gastroenteritis (0.3%). Across the submitted studies of individuals 2 through 23 months of age, within 28 days of vaccination, two deaths were reported in the Menveo treatment groups (one case of sudden death and one case of sepsis), while no deaths were reported in the control group. None of the deaths was assessed as related to vaccination. Among subjects with symptom onset within 42 days of vaccination (days 12, 25, 29), 3/12049 [0.02%, 95% CI: (0.01%, 0.07%)] Menveo recipients and 0/2877 [0%, 95% CI: (0%, 0.13%)] control recipients were diagnosed with Kawasaki Disease. One case of acute disseminated encephalomyelitis with symptom onset 29 days post-dose 4 was observed in a participant given Menveo co-administered with routine US childhood vaccines at 12 months of age (including MMR and varicella vaccines).

The information regarding serious adverse events in subjects 2 years through 10 years of age was derived from 3 randomized, controlled clinical trials 7-9. Safety follow-up ranged from 6 months through 12 months and included 2883 subjects administered Menveo. Serious adverse events reported during the safety follow-up periods occurred in 21/2883 (0.7%) of Menveo subjects, in 7/1255 (0.6%) of ACWY-D subjects, and 2/861 (0.2%) of ACWY-PS subjects. In the subjects receiving either one or two doses of Menveo, there were 6 subjects with pneumonia, 3 subjects with appendicitis and 2 subjects with dehydration; all other events were reported to occur in one subject. Among 1255 subjects administered a single dose of ACWY-D and 861 subjects administered

ACWY-PS, there were no events reported to occur in more than one subject. The serious adverse events occurring within the first 30 days after receipt of each vaccine were as follows: Menveo (6/2883 [0.2%]) – appendicitis, pneumonia, staphylococcal infection, dehydration, febrile convulsion, and tonic convulsion; ACWY-D (1/1255 [0.1%]) – inguinal hernia; ACWY-PS (2/861 [0.2%]) – abdominal pain, lobar pneumonia. In a supportive study 6, 298 subjects received one or two doses of Menveo and 22 (7%) had serious adverse events over a 13-month follow-up period including 13 subjects with varicella and 2 subjects with laryngitis. All other events were reported to occur in one subject. During the 30 days post vaccination in this study, one limb injury and one case of varicella were reported.

The information regarding serious adverse events in subjects 11 years through 55 years of age was derived from 5 randomized, controlled clinical trials 10-14. Serious adverse events reported within 6 months of vaccination occurred in 40/6185 (0.6%) of Menveo subjects, 13/1757 (0.7%) of ACWY-D subjects, and 5/209 (2.4%) of ACWY-PS subjects. During the 6 months following immunization, serious adverse events reported by more than one subject were as follows: Menveo - appendicitis (3 subjects), road traffic accident (3 subjects), and suicide attempt (5 subjects); ACWY-D - intervertebral disc protrusion (2 subjects); ACWY- PS - none. Serious adverse events that occurred within 30 days of vaccination were reported by 7 of 6185 (0.1%) subjects in the Menveo group, 4 of 1757 (0.2%) subjects in the ACWY- D group, and by none of 209 subjects in the ACWY-PS group. The events that occurred during the first 30 days post immunization with Menveo were: vitello-intestinal duct remnant; Cushing's syndrome; viral hepatitis; pelvic inflammatory disease; intentional multiple drug overdose; simple partial seizure; and suicidal depression. The events that occurred during the first 30 days post immunization with ACWY-D were: herpes zoster; fall; intervertebral disc protrusion; and angioedema.

Adverse reactions from post-marketing spontaneous reports

Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish, for all events, a causal relationship to vaccine exposure.

Individuals 11 to 65 years of age

Ear and labyrinth disorders: hearing impaired, ear pain, vertigo, vestibular disorder.
Eye disorders: eyelid ptosis.
General disorders and administration site conditions: injection site cellulitis, injection site pruritus, pain, erythema, inflammation and swelling, including extensive swelling of the injected limb, fatigue, malaise, pyrexia.
Immune system disorders: hypersensitivity including anaphylaxis.
Injury, poisoning and procedural complications: fall, head injury.
Investigation: alanine aminotransferase increased, body temperature increased.
Musculoskeletal and connective tissue disorders: arthralgia, bone pain.
Nervous system disorders: dizziness, syncope, tonic convulsion, headache, facial paresis, balance disorder.
Respiratory, thoracic and mediastinal disorders: oropharyngeal pain.
Skin and subcutaneous tissue disorders: bullous conditions.

Children 2 to 10 years of age

General disorders and administration site conditions: injection site swelling,

including extensive swelling of the injected limb.
Nervous system disorders: febrile convulsion

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Meningococcal vaccines, ATC code:

J07AH08. Immunogenicity

The efficacy of Menveo has been inferred by measuring the production of serogroup-specific anti-capsular antibodies with bactericidal activity. Serum bactericidal activity (SBA) was measured using human serum as the source of exogenous complement (hSBA). The hSBA was the original correlate of protection against meningococcal disease.

Immunogenicity was evaluated in randomized, multicenter, active controlled clinical trials that enrolled persons from 2 months through 65 years of age.

Immune responses following a 4-dose infant series (2 months through 16 months of age)

The pre-specified endpoint for immunogenicity of Menveo in infants receiving a 4-dose series at 2, 4, 6 and 12 months of age was the proportion of subjects achieving an hSBA ≥ 1:8, with the lower limit of the 2-sided 95% CI for the point estimate being ≥ 80% of vaccinees for serogroup A, and ≥ 85% of vaccinees for serogroups C, W-135 and Y one month following the final dose. Sera were obtained at 2 months (prior to the first infant dose), at 7 months (1 month after the infant series), 12 months (prior to the older infants dose), and 13 months of age (1 month after the final dose) which allowed evaluation of the immunogenicity of the infant series as well as of the complete series. The immunogenicity of Menveo in infants was assessed in two pivotal randomized, controlled, multicenter studies of infants, who received a 4-dose series at 2, 4, 6 and 12 months of age and subjects who received a 4-dose series at 2, 4, 6, and 16 months of age.

The pre-defined criteria for immunogenicity were met for all four serogroups A, C, W-135 and Y at one month following completion of a 4-dose series at 2, 4, 6 and 12 months (Table 1).

Table 1: Bactericidal antibody responses following administration of Menveo with routine paediatric vaccines at 2, 4, 6 and 12 months of age

Serogroup		Post 3rd dose	Post 4th dose
		N=202	N=168
A	% ≥1:8 95% CI	76 (69, 81)	89 (83[a], 93)

	GMT 95% CI	21 (17, 26)	54 (44, 67)
C		**N=199**	**N=156**
	% ≥1:8 95% CI	94 (90, 97)	95 (90 [a], 98)
	GMT 95% CI	74 (62, 87)	135 (107, 171)
W-135		**N=194**	**N=153**
	% ≥1:8 95% CI	98 (95, 99)	97 (93 [a], 99)
	GMT 95% CI	79 (67, 92)	215 (167, 227)
Y		**N=188**	**N=153**
	% ≥1:8 95% CI	94 (89, 97)	96 (92 [a], 99)
	GMT 95% CI	51 (43, 61)	185 (148, 233)

% ≥1:8 = proportions of subjects with hSBA ≥ 1:8 against a given serogroup; CI = confidence interval; GMT = geometric mean antibody titer; N = number of infants eligible for inclusion in the Per-Protocol Immunogenicity population for whom serological results were available for the post-dose 3 and post-dose 4 evaluations.
Serum Bactericidal Assay with exogenous human complement source (hSBA).
[a] Prespecified criteria for adequacy of immune response were met (lower limit of the 95% CI > 80% for serogroup A and > 85% for serogroups C, W, and Y).

Immune responses following a 2-dose series in children 6 months through 23 months of age.

The immunogenicity of Menveo was assessed in children, who did not receive the 4-dose series but instead received 2 dose series. Among the per protocol population of 386 subjects, after Menveo administered at 7-9 and at 12 months, the proportions of subjects with hSBA ≥
1:8 for serogroups A, C, W-135, and Y were respectively: 88% (84-91), 100% (98-100), 98% (96-100), 96% (93-99).

Immunogenicity in children

In the pivotal study V59P20 immunogenicity of Menveo was compared to ACWY-D; 1170 children were vaccinated with Menveo and 1161 received the comparator vaccine in the per protocol populations. In two supportive studies V59P8 and V59P10 immunogenicity of Menveo was compared to ACWY-PS.

In the pivotal, randomized, observer-blind study V59P20, in which participants were stratified by age (2 through 5 years and 6 through 10 years), the immunogenicity of a single dose of Menveo one month post vaccination was compared with the single dose of ACWY- D. In both age groups, non-inferiority of Menveo to ACWY-D for the proportion of subjects with a seroresponse and percentage of subjects with hSBA ≥1:8 was demonstrated for serogroups C, W-135 and Y, but not for serogroup A. For both age groups (2-5 years and 6-10 years of age), the immune response as measured by hSBA GMTs was non-inferior for all serogroups (Table 2). In addition, the percentage of

subjects with a seroresponse, percentage of subjects with hSBA ≥1:8, and GMT levels were statistically higher among Menveo recipients for serogroups W-135 and Y. GMT levels were also statistically higher among Menveo recipients for serogroup C.

Table 2: Comparison of serum bactericidal antibody responses to Menveo and ACWY-D 1 month after vaccination of subjects 2 through 10 years of age

	2-5			6-10			2-10		
Endpoint by Serogroup	**Menveo (95% CI)**	**ACWY-D (95% CI)**	**Percent Difference (Menveo – ACWY-D) or GMT ratio (Menveo/ ACWY-D) (95% CI)**	**Menveo (95% CI)**	**ACWY-D (95% CI)**	**Percent Difference (Menveo – ACWY-D) or GMT ratio (Menveo/ ACWY-D) (95% CI)**	**Menveo (95% CI)**	**ACWY-D (95% CI)**	**Percent Difference (Menveo – ACWY-D) or GMT ratio (Menveo/ ACWY-D) (95% CI)**
A	N=606	N=611		N=551	N=541		N=1157	N=1152	
% Seroresponse‡	72 (68, 75)	77 (73, 80)	-5 (-10.0, -0.3)	77 (73, 80)	83 (79, 86)	-6 (-11, -1)	74 (71,76)	80 (77,82)	-6* (-9, -2)
% ≥1:8	72 (68, 75)	78 (74, 81)	-6 (-11, -1)	77 (74, 81)	83 (80, 86)	-6 (-11, -1)	75 (72, 77)	80 (78, 83)	-6* (-9,-3)
GMT	26 (22, 30)	25 (21, 29)	1.04* (0.86, 1.27)	35 (29, 42)	35 (29, 41)	1.01* (0.83, 1.24)	30 (27, 34)	29 (26, 33)	1.03* (0.89,1.18)
C	N=607	N=615		N=554	N=539		N=1161	N=1154	
% Seroresponse‡	60 (56, 64)	56 (52, 60)	4 * (-2, 9)	63 (59, 67)	57 (53, 62)	6* (0, 11)	61 (58, 64)	57 (54, 60)	5* § (1, 9)
% ≥1:8	68 (64, 72)	64 (60, 68)	4* (-1, 10)	77 (73, 80)	74 (70, 77)	3* (-2, 8)	72 (70, 75)	68 (66, 71)	4* (0, 8)
GMT	18 (15, 20)	13 (11, 15)	1.33* § (1.11, 1.6)	36 (29, 45)	27 (21, 33)	1.36* § (1.06, 1.73)	23 (21, 27)	17 (15, 20)	1.34* § (1.15, 1.56)
W-135	N=594	N=605		N=542	N=533		N=1136	N=1138	
% Seroresponse‡	72 (68, 75)	58 (54, 62)	14 * § (9, 19)	57 (53, 61)	44 (40, 49)	13* § (7, 18)	65 (62, 67)	51 (48, 54)	13* § (9, 17)
% ≥1:8	90 (87, 92)	75 (71, 78)	15* § (11, 19)	91 (88, 93)	84 (81, 87)	7* § (3, 11)	90 (88, 92)	79 (77, 81)	11* § (8, 14)
GMT	43 (38, 50)	21 (19, 25)	2.02* § (1.71, 2.39)	61 (52, 72)	35 (30, 42)	1.72* § (1.44, 2.06)	49 (44, 54)	26 (23, 29)	1.87* § (1.65, 2.12)
Y	N=593	N=600		N=545	N=539		N=1138	N=1139	
% Seroresponse‡	66 (62, 70)	45 (41, 49)	21 * § (16, 27)	58 (54, 62)	39 (35, 44)	19* § (13, 24)	62 (60, 65)	42 (40, 45)	20* § (16, 24)
% ≥1:8	76 (72, 79)	57 (53, 61)	19* § (14, 24)	79 (76, 83)	63 (59, 67)	16* § (11, 21)	77 (75, 80)	60 (57, 63)	18* § (14, 21)
GMT	24 (20, 28)	10 (8.68, 12)	2.36* § (1.95, 2.85)	34 (28, 41)	14 (12, 17)	2.41* § (1.95, 2.97)	29 (25, 32)	12 (11, 14)	2.37* § (2.06, 2.73)

‡ Seroresponse was defined as: a) post vaccination hSBA ≥1:8 for subjects with a pre-vaccination hSBA <1:4; or, b) at least
4-fold higher than baseline titers for subjects with a pre-vaccination hSBA ≥1:4.
* Non-inferiority criterion met (the lower limit of the two-sided 95% CI >-10 % for vaccine group differences [Menveo minus ACWY-D] and > 0.5 for ratio of GMTs [Menveo/ACWY-D]).
§ Immune response was statistically higher (the lower limit of the two-sided 95% CI >0% for vaccine group differences or >
1.0 for ratio of GMTs); however the clinical relevance of higher post-vaccination immune responses is not known

In another randomized, observer-blind study (V59P8) US children were immunized with a single dose of either Menveo (N=284) or ACWY-PS (N=285). In the children 2-10 years of age, as well as in each age strata (2-5 and 6-10 years), immune response as measured by percentage of subjects with seroresponse, hSBA≥1:8 and GMTs were not

only non-inferior to comparator vaccine ACWY-PS, but all were statistically higher than the comparator for all serogroups and all immune measurements at 1 month post vaccination. At 1 year post vaccination, Menveo continued to be statistically higher than ACWY-PS for serogroups A, W-135 and Y, as measured by percentage of subjects with hSBA≥1:8 and GMTs. Menveo was non-inferior on these endpoints for serogroup C (Table 3).

Table 3: Comparison of serum bactericidal antibody responses to Menveo and ACWY-PS 1 month and 12 months after vaccination of subjects 2 through 10 years of age

Endpoint by Serogroup	**Menveo (95% CI)**	**ACWY-PS (95% CI)**	**Percent Difference (Menveo – ACWY-PS) or GMT ratio (Menveo/ACWY-PS)(95% CI)**	**Menveo (95% CI)**	**ACWY-PS (95% CI)**	**Percent Difference (Menveo – ACWY-PS) or GMT ratio (Menveo/ACWY-PS)(95% CI)**
	1 month post-vaccination			12 months post-vaccination		
A	N=280	N=281		N=253	N=238	
Seroresponse‡	79 (74, 84)	37 (31, 43)	43*§ (35,50)	n/a	n/a	
% ≥1:8	79 (74, 84)	37 (31, 43)	42*§ (35, 49)	23 (18, 29)	13 (9, 18)	10 *§ (3, 17)
GMT	36 (30, 44)	6.31 (5.21, 7.64)	5.74*§ (4.38, 7.53)	3.88 (3.39, 4.44)	3 (2.61, 3.44)	1.29*§ (1.07, 1.57)
C	N=281	N=283		N=252	N=240	
Seroresponse‡	64 (59, 70)	43 (38, 49)	21*§ (13, 29)	n/a	n/a	
% ≥1:8	73 (68, 78)	54 (48, 60)	19*§ (11, 27)	53 (47, 59)	44 (38, 51)	9* (0, 18)
GMT	26 (21, 34)	15 (12, 20)	1.71*§ (1.22, 2.40)	11 (8.64, 13)	9.02 (7.23, 11)	1.19* (0.87, 1.62)
W-135	N=279	N=282		N=249	N=237	
Seroresponse‡	67 (61, 72)	31 (26, 37)	35*§ (28, 43)	n/a	n/a	
% ≥1:8	92 (88, 95)	66 (60, 71)	26*§ (20, 33)	90 (86, 94)	45 (38, 51)	46 *§ (38, 53)
GMT	60 (50, 71)	14 (12, 17)	4.26*§ (3.35, 5.43)	42 (35, 50)	7.57 (6.33, 9.07)	5.56*§ (4.32, 7.15)
Y	N=280	N=282		N=250	N=239	
Seroresponse‡	75 (70, 80)	38 (32, 44)	37 *§ (30, 45)	n/a	n/a	
% ≥1:8	88 (83, 91)	53 (47, 59)	34*§ (27, 41)	77 (71, 82)	32 (26, 38)	45 *§ (37, 53)
GMT	54 (44, 66)	11 (9.29, 14)	4.70 *§ (3.49, 6.31)	27 (22, 33)	5.29 (4.34, 6.45)	5.12 *§ (3.88, 6.76)

‡ Seroresponse was defined as: a) post vaccination hSBA ≥1:8 for subjects with a pre-vaccination hSBA <1:4; or, b) at least
4-fold higher than baseline titers for subjects with a pre-vaccination hSBA ≥1:4.
* Non-inferiority criterion met (the lower limit of the two-sided 95% CI >-10 % for vaccine group differences [Menveo minus ACWY-PS] and > 0.5 for ratio of GMTs [Menveo/ACWY-PS]).
§ Immune response was statistically higher (the lower limit of the two-sided 95% CI >0% for vaccine group differences or >
1.0 for ratio of GMTs); however the clinical relevance of higher post-vaccination immune responses is not known. n/a = not applicable

In a randomized, observer-blind study (V59P10) conducted in Argentina, children were immunized with a single dose of either Menveo (N=949) or ACWY-PS (N=551). Immunogenicity was assessed in a subset of 150 subjects in each vaccine group. The immune response observed in the children 2-10 years of age was very similar to those observed in the V59P8 study shown above: immune response to Menveo at 1 month post vaccination, as measured by percentage of subjects with seroresponse, hSBA≥1:8 and GMTs, was non-inferior to ACWY-PS.

Immunogenicity in adolescents

In the pivotal study (V59P13), adolescents or adults received either a dose of Menveo (N = 2649) or quadrivalent, diphtheria toxoid conjugated, meningococcal vaccine as comparator (ACWY-D) (N = 875). Sera were obtained both before vaccination and 1 month after vaccination.

In another study (V59P6) conducted in 524 adolescents, the immunogenicity of Menveo was compared to that of ACWY-PS.

In the 11-18 year old population of the pivotal study, V59P13, the immunogenicity of a single dose of Menveo one month post vaccination is compared with the quadrivalent, ACWY-Diphtheria toxoid protein conjugate vaccine (ACWY-D). Immunogenicity results at one month after Menveo are summarized below in Table 4.

Non-inferiority of Menveo to ACWY-D was demonstrated for all four serogroups using the primary endpoint (hSBA seroresponse). The percentages of subjects with hSBA seroresponse, the percentage of subjects with hSBA ≥ 1:8 and the ratio of GMTs were statistically higher for serogroups A, W-135, and Y in the Menveo group, as compared to the ACWY-D group (Table 4).

Table 4: Serum bactericidal antibody responses following Menveo one month after vaccination among subjects aged 11-18 years

Serogroup	Menveo (95% CI)	ACWY-D (95% CI)	Menveo/ ACWY-D (95% CI)	Menveo minus ACWY-D (95% CI)
A	N=1075	N=359		
% Seroresponse‡	75 (72, 77)	66 (61, 71)		8 (3, 14)*§
% ≥ 1:8	75 (73, 78)	67 (62, 72)	-	8 (3, 14)*§
GMT	29 (24, 35)	18 (14, 23)	1.63 (1.31, 2.02)*§	-
C	N=1396	N=460		
% Seroresponse‡	76 (73, 78)	73 (69, 77)		2 (-2, 7)*
% ≥ 1:8	85 (83, 87)	85 (81, 88)	-	0 (-4, 4)*
GMT	50 (39, 65)	41 (30, 55)	1.22 (0.97, 1.55)*	-
W-135	N=1024	N=288		
% Seroresponse‡	75 (72, 77)	63 (57, 68)		12 (6, 18)*§

% ≥ 1:8	96 (95, 97)	88 (84, 92)	-	8 (4, 12)*§
GMT	87 (74, 102)	44 (35, 54)	2.00 (1.66, 2.42)*§	-
Y	N=1036	N=294		
% Seroresponse‡	68 (65, 71)	41 (35, 47)		27 (20, 33)*§
% ≥ 1:8	88 (85, 90)	69 (63, 74)	-	19 (14, 25)*§
GMT	51 (42, 61)	18 (14, 23)	2.82 (2.26, 3.52)*§	-

‡ Seroresponse was defined as: a) post vaccination hSBA ≥1:8 for subjects with a pre-vaccination hSBA <1:4; or, b) at least 4-fold higher than baseline titers for subjects with a pre-vaccination hSBA ≥1:4.
* Non-inferiority criterion for the primary endpoint met (the lower limit of the two-sided 95% CI >-10 % for vaccine group differences [Menveo minus ACWY-D] and > 0.5 for ratio of GMTs [Menveo/ACWY-D]).
§ Immune response was statistically higher (the lower limit of the two-sided 95% CI >0% for vaccine group differences or > 1.0 for ratio of GMTs); however the clinical relevance of higher post-vaccination immune responses is not known.

In the subset of subjects aged 11-18 years who were seronegative at baseline (hSBA < 1:4), the proportion of subjects who achieved a hSBA ≥ 1:8 after a dose of Menveo were as follows: serogroup A 75% (780/1039); serogroup C 80% (735/923); serogroup W-135 94% (570/609); serogroup Y 81% (510/630).

The persistence of immune responses for Menveo at 21 months post vaccination among a subset of subjects aged 11-18 years at the time of vaccination is shown in Table 5.

Table 5: Persistence of immune responses approximately 21 months after vaccination with Menveo (subjects were aged 11-18 years at the time of vaccination)

Endpoint by Serogroup	**Menveo (95% CI)**	**ACWY-D (95% CI)**	**Naive‡ (95% CI)**
A	N=275	N=179	N=97
% ≥1:8	36 (30, 42)	23 (17, 30)	5 (2, 12)
GMT	5.29 (4.63, 6.05)	3.5 (2.97, 4.14)	2.36 (1.88, 2.96)
C	N=275	N=179	N=97
% ≥1:8	62 (56, 68)	59 (52, 66)	42 (32, 53)
GMT	10	8.96	5.95
	(9.02, 12)	(7.51, 11)	(4.68, 7.56)
W-135	N=273	N=176	N=97
% ≥1:8	84 (79,	74 (67,	51 (40,
GMT	18 (15,	14 (12,	7.80
Y	N=275	N=179	N=97
% ≥1:8	67 (61,	54 (47,	40 (30,
GMT	12 (10,	7.85	5.14

‡ Age matched subjects not previously immunized with meningococcal vaccine

In the non-inferiority study, V59P6, immunogenicity was assessed among adolescents aged 11-17 years who had been randomized to receive either Menveo or quadrivalent meningococcal polysaccharide vaccine (ACWY-PS). For all four serogroups (A, C, W-135 and Y) Menveo was shown to be non-inferior to ACWY-PS vaccine based on

seroresponse, proportions achieving hSBA ≥1:8, and GMTs, and statistically higher based on seroresponse and GMTs. In addition, Menveo was statistically higher to ACWY-PS for serogroups A, C and Y in the percentage of subjects with post vaccination hSBA ≥ 1:8 (Table 6).

Table 6: Immunogenicity of one dose of Menveo or ACWY-PS in adolescents, measured at one month post vaccination

	hSBA ≥1:8 (95% CI)		hSBA GMTs (95% CI)	
Serogroup	**Menveo**	**ACWY-PS**	**Menveo**	**ACWY-PS**
A	N=140	N=149	N=140	N=149
	81% (74, 87)	41% (33, 49)	33 (25, 44)	7.31 (5.64, 9.47)
C	N=140	N=147	N=140	N=147
	84% (77, 90)	61% (53, 69)	59 (39, 89)	28 (19, 41)
W	N=138	N=141	N=138	N=141
	91% (84, 95)	84% (77, 89)	48 (37, 62)	28 (22, 36)
Y	N=139	N=147	N=139	N=147
	95% (90, 98)	82% (75, 88)	92 (68, 124)	35 (27, 47)

At one year post vaccination, the percentage of Menveo recipients with hSBA ≥ 1:8 remained statistically higher compared with ACWY-PS recipients for serogroups C, W-135 and Y, and similar between the two study groups for serogroup A. Similar findings were observed in the comparison of hSBA GMTs.

Immunogenicity in adults

In the pivotal immunogenicity trial, V59P13, immune responses to Menveo were assessed among adults aged 19 to 55 years. Results are presented in Table 7. Non-inferiority of Menveo to ACWY-D was demonstrated for all four serogroups using the primary endpoint (hSBA seroresponse) (Table 7).

Table 7: Serum bactericidal antibody responses following Menveo one month after vaccination among subjects aged 19-55 years

Endpoint by Serogroup	Menveo (95% CI)	ACWY-D (95% CI)	Menveo /ACWY-D (95% CI)	Menveo minus ACWY-D (95% CI)
A	N=963	N=321		
% Seroresponse[‡]	67 (64, 70)	68 (63, 73)		-1 (-7, 5)*
% ≥ 1:8	69 (66, 72)	71 (65, 76)	-	-2 (-7, 4)*
GMT	31 (27, 36)	30 (24, 37)	1.06 (0.82, 1.37)*	-
C	N=902	N=300		
% Seroresponse[‡]	68 (64, 71)	60 (54, 65)		8 (2, 14)* [§]

% ≥ 1:8	80 (77, 83)	74 (69, 79)	-	6 (1, 12)*§
GMT	50 (43, 59)	34 (26, 43)	1.50 (1.14, 1.97)*§	-
W-135	N=484	N=292		
% Seroresponse‡	50 (46, 55)	41 (35, 47)		9 (2, 17)*§
% ≥ 1:8	94 (91, 96)	90 (86, 93)	-	4 (0, 9)*
GMT	111 (93, 132)	69 (55, 85)	1.61 (1.24, 2.1)*§	-
Y	N=503	N=306		
% Seroresponse‡	56 (51, 60)	40 (34, 46)		16 (9, 23)*§
% ≥ 1:8	79 (76, 83)	70 (65, 75)	-	9 (3, 15)*§
GMT	44 (37, 52)	21 (17, 26)	2.10 (1.60, 2.75)*§	-

‡ Seroresponse was defined as: a) post vaccination hSBA ≥1:8 for subjects with a pre-vaccination hSBA <1:4; or, b) at least 4-fold higher than baseline titers for subjects with a pre-vaccination hSBA ≥1:4.
* Non-inferiority criterion met (the lower limit of the two-sided 95% CI >-10 % for vaccine group differences [Menveo minus ACWY-D] and > 0.5 for ratio of GMTs [Menveo/ACWY-D]).
§ Immune response was statistically higher (the lower limit of the two-sided 95% CI >0% for vaccine group differences or > 1.0 for ratio of GMTs); however the clinical relevance of higher post-vaccination immune responses is not known.

In the subset of subjects aged 19-55 years who were seronegative at baseline, the proportion of subjects who achieved a hSBA ≥ 1:8 after a dose of Menveo were as follows: serogroup A 67% (582/875); serogroup C 71% (401/563); serogroup W-135 82% (131/160); serogroup Y 66% (173/263).

Immunogenicity in older adults

The comparative immunogenicity of Menveo vs. ACWY-PS was evaluated in subjects aged 56-65 years, in study V59P17. The proportion of subjects with hSBA ≥ 1:8 was non-inferior to ACWY-PS for all four serogroups and statistically higher for serogroups A and Y.

Table 8: Immunogenicity of one dose of Menveo or ACWY-PS in adults aged 56-65 years, measured at one month post vaccination.

Serogroup	**Menveo hSBA ≥ 1:8 (95% CI)**	**ACWY-PS hSBA ≥ 1:8 (95% CI)**
A	N=83	N=41
	87% (78, 93)	63% (47, 78)
C	N=84	N=41
	90% (82, 96)	83% (68, 93)
W	N=82	N=39
	94% (86, 98)	95% (83, 99)
Y	N=84	N=41
	88% (79, 94)	68% (52, 82)

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional repeated- dose and reproductive and developmental toxicity studies.
In laboratory animals, no adverse reactions were seen in vaccinated maternal rabbits or in their offspring through postnatal day 29.
No effects on fertility were observed in female rabbits receiving Menveo pre-mating and during pregnancy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients and trace residues

Powder
Sucrose
Potassium dihydrogen phosphate

Solution

Sodium dihydrogen phosphate monohydrate
Disodium phosphate dihydrate
Sodium chloride
Water for injections

Residual formaldehyde per dose is estimated to be not more than 0.3 micrograms.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

36 months

After reconstitution, the product should be used immediately. However, chemical and physical stability after reconstitution was demonstrated for 8 hours below 25°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.
Keep the vials in the outer carton in order to protect from light.

For storage conditions of the reconstituted product, see section 6.3.

6.5 Nature and contents of container

Powder in vial (type I glass) with a stopper (halobutyl rubber) and solution in vial (type I glass) with a stopper (butyl rubber).

The contents of the two components (powder vial and solution vial) are to be mixed prior to vaccination providing one dose of 0.5 ml.

Pack size of one dose (2 vials) or five doses (10 vials).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The contents of the two components in the two different containers (MenA powder and MenCWY solution) are to be mixed prior to vaccination providing 1 dose of 0.5 ml.

Menveo must be prepared for administration by reconstituting powder (in vial) with solution (in vial).

The components of the vaccine should be visually inspected before and after reconstitution.

Using a syringe and suitable needle (21G, 1 ½ inch length or a 21G, 40 mm length), withdraw the entire contents of the vial of solution and inject into the vial of powder to reconstitute the MenA conjugate component.

Invert and shake the vial vigorously and then withdraw 0.5 ml of reconstituted product. Please note that it is normal for a small amount of liquid to remain in the vial following withdrawal of the dose.

Following reconstitution, the vaccine is a clear, colourless to light yellow solution, free from visible foreign particles. In the event of any foreign particulate matter and/or variation of physical aspect being observed, discard the vaccine.

Prior to injection, change the needle for one suitable for the administration. Ensure that no air bubbles are present in the syringe before injecting the vaccine.

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

Product Registrant

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Version: CDS 4.3

[GSK logo]