

## 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 <i>Corynebacterium diphtheriae</i> CRM <sub>197</sub> protein	16.7 to 33.3 micrograms

(Originally contained in the solution)

• Meningococcal group C oligosaccharide	5 micrograms
Conjugated to <i>Corynebacterium diphtheriae</i> CRM <sub>197</sub> protein	7.1 to 12.5 micrograms
• Meningococcal group W-135 oligosaccharide	5 micrograms
Conjugated to <i>Corynebacterium diphtheriae</i> CRM <sub>197</sub> protein	3.3 to 8.3 micrograms
• Meningococcal group Y oligosaccharide	5 micrograms
Conjugated to <i>Corynebacterium diphtheriae</i> CRM <sub>197</sub> 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

Infants initiating vaccination from 2 to 6 months of age

First 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 to 16 months).

Alternatively, when Menveo is given as part of a routine infant immunisation programme or according to a national recommendation, a series consisting of three doses, each of 0.5ml, may be given. The first dose should be administered from the age of 2 months, with a second dose 2 months later. The third dose should be administered as early as possible during the second year of life (see section 5.1).

If optimal protection against serogroup A is required (for example, travellers to areas where serogroup A is endemic), a 4-dose schedule should be used (see Section 4.4 Special warnings and precautions for use).

Infants with medical conditions associated with increased risk of invasive meningococcal disease should receive a 4-dose schedule (see Section 4.4 Special warnings and precautions for use).

#### 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

Menveo may be given as a booster dose in subjects who have previously received primary vaccination with Menveo, other conjugated meningococcal vaccine or meningococcal unconjugated polysaccharide vaccine. The need for and timing of a booster dose in subjects previously vaccinated with Menveo is to be defined based on national recommendations.

#### Elderly

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

#### Method of administration

Each Menveo dose is to be administered as a single 0.5 ml 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<sub>197</sub>), 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. Menveo has not been evaluated in the immunocompromised; individuals with HIV infection, 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.

Individuals receiving treatment that inhibits terminal complement activation (for example, eculizumab) remain at increased risk of invasive disease caused by *Neisseria meningitidis* groups A, C, W-135 and Y even following vaccination with Menveo.

In infants initiating vaccination from 2 to 6 months of age:

If the optimal protection against serogroup A is required (for example, travellers to areas where serogroup A is endemic), a 4-dose schedule should be used. Infants with medical conditions associated with increased risk of invasive meningococcal disease should receive a 4-dose schedule.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Menveo can be given concomitantly with meningococcal group B vaccine (Bexsero).

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

In children from 2 to 23 months of age vaccinated in clinical trials, Menveo was administered concomitantly with vaccines containing the following antigens: diphtheria toxoid, acellular pertussis, tetanus toxoid, *Haemophilus influenzae* type b (Hib), inactivated polio, hepatitis B (HBV), inactivated hepatitis A, 7-valent and 13-valent pneumococcal conjugate vaccine capsular antigens (PCV7 and PCV13), pentavalent rotavirus, and measles, mumps, rubella and varicella viruses (MMRV). No increase in the reactogenicity or change in the safety profile of the routine vaccines was observed.

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 third study of infants initiating vaccination at 2 months of age, Menveo was given concomitantly at 2, 4 and 6 months with routine infant vaccines including 13-valent pneumococcal conjugate vaccine.

In a clinical trial of children ( $\geq 7$  months of age), 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.

No immune interference was observed for the concomitantly administered vaccines with exception of pneumococcal vaccine serotype 6B in one study, and against pneumococcal vaccine serotype 19A in another study, both 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 $\geq$ 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: monovalent and combined hepatitis A and B, yellow fever, typhoid fever (Vi polysaccharide), Japanese encephalitis and rabies. The concomitant administration of Menveo with hepatitis A and B vaccines, 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: ( $\geq 1/10$ )  
Common: ( $\geq 1/100$  to  $< 1/10$ )  
Uncommon: ( $\geq 1/1,000$  to  $< 1/100$ )  
Rare: ( $\geq 1/10,000$  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 4.5). 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. The most common local reaction was tenderness at injection site, while for systemic reactions, irritability and sleepiness were the most common. The highest rate of solicited reactions occurred after the first dose in both treatment groups.

A similar safety profile was observed among 476 infants who completed a 3-dose infant series, including 297 who received doses at 2, 6 and 12 months and 179 who received doses at 2, 4 and 12 months of age.

The safety of Menveo with 2-dose schedule was assessed in 1985 children immunized between 6 and 23 months of age in three randomized studies that addressed the safety of

Menveo administered concomitantly with routine paediatric vaccines. Common solicited adverse reactions ( $\geq 10\%$ ) 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 ( $\leq 50$  mm), injection site induration ( $\leq 50$  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 characterization of the safety profile of Menveo in children 2 to 10 years of age is based on data from 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 ( $\leq 50$  mm), injection site induration ( $\leq 50$  mm)

Common: injection site erythema ( $> 50$  mm), injection site induration ( $> 50$  mm), chills, fever  $\geq 38^{\circ}\text{C}$

Uncommon: injection site pruritus

Individuals 11 to 65 years of age

The characterization of the safety profile of Menveo in adolescents and adults is based on data from five randomized controlled clinical trials including 6401 participants (from 11-65 years of age. Among Menveo recipients, 58.9%, 16.4%, 21.3% and 3.4% were in the 11 to 18 year, 19 to 34 year, 35 to 55 year and 56 to 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 to 65 years who received Menveo (N=216), were similar to that observed in Menveo recipients subjects aged 11 to 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 ( $\leq 50$  mm), injection site



induration ( $\leq 50$  mm), malaise

Common: injection site erythema ( $> 50$  mm), injection site induration ( $> 50$  mm), fever  $\geq 38^{\circ}\text{C}$ , 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 (all age groups)**

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.

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.

Blood and lymphatic system disorders: local lymphadenopathy

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, febrile

convulsion, headache, facial paresis, balance disorder.  
Respiratory, thoracic and mediastinal disorders: oropharyngeal pain.  
Skin and subcutaneous tissue disorders: bullous conditions.

## 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 $\geq$ 1:8, with the lower limit of the 2-sided 95% CI for the point estimate being  $\geq$ 80% of vaccinees for serogroup A, and  $\geq$ 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 3 <sup>rd</sup> dose	Post 4 <sup>th</sup> dose

<b>A</b>		<b>N=202</b>	<b>N=168</b>
	% ≥1:8 95% CI	76 (69, 81)	89 (83 <sup>a</sup> , 93)
	GMT 95% CI	21 (17, 26)	54 (44, 67)
<b>C</b>		<b>N=199</b>	<b>N=156</b>
	% ≥1:8 95% CI	94 (90, 97)	95 (90 <sup>a</sup> , 98)
	GMT 95% CI	74 (62, 87)	135 (107, 171)
<b>W-135</b>		<b>N=194</b>	<b>N=153</b>
	% ≥1:8 95% CI	98 (95, 99)	97 (93 <sup>a</sup> , 99)
	GMT 95% CI	79 (67, 92)	215 (167, 227)
<b>Y</b>		<b>N=188</b>	<b>N=153</b>
	% ≥1:8 95% CI	94 (89, 97)	96 (92 <sup>a</sup> , 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).

<sup>a</sup> 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 3-dose infant series (2 months through 12 months of age)

In study V59\_36, children 2 months of age at enrolment were administered either 4 doses at 2, 4, 6 and 12 months of age or 3 doses at 2, 4 and 12 months of age. By one month after the second vaccination (5 months of age), substantial increases in immune responses were seen for all 4 serogroups. The 3-dose series was shown to be non-inferior to the 4-dose series for serogroups C, W-135 and Y at 1 month after the 12 month vaccination. The hSBA GMTs at 13 months were also similar between the 3-dose and 4-dose groups for serogroups C, W-135 and Y (Table 2). Although immune responses to serogroup A were not included in the non-inferiority assessment, a relevant proportion of participants (88%) achieved seroprotective (hSBA titre ≥1:8) titre one month following the 3-dose primary schedule. Long term antibody persistence was not measured in this study.

**Table 2: Bactericidal antibody responses following a 3-dose (2, 4 and 12 months) and a 4-dose infant series of Menveo with routine paediatric vaccines**

<b>Serogroup</b>	<b>Percentages of Subjects with hSBA ≥1:8</b>				<b>hSBA GMTs</b>			
	<b>Menveo 3-dose</b>		<b>Menveo 4-dose</b>		<b>Menveo 3-dose</b>		<b>Menveo 4-dose</b>	
	<u>5 months</u>	<u>13 months</u>	<u>7 months</u>	<u>13 months</u>	<u>5 months</u>	<u>13 months</u>	<u>7 months</u>	<u>13 months</u>
<b>A</b>	<u>N=157</u>	<u>N=146</u>	<u>N=157</u>	<u>N=141</u>	<u>N=157</u>	<u>N=146</u>	<u>N=157</u>	<u>N=141</u>

	<u>43</u> (35-51)	<u>88</u> (82-93)	<u>84</u> (77-89)	<u>96</u> (91-98)	<u>7.09</u> (5.62- 8.94)	<u>59</u> (45-77)	<u>28</u> (23-35)	<u>94</u> (76-117)
<u>C</u>	<u>N=170</u> <u>86</u> (80-91)	<u>N=160</u> <u>95*</u> (90-98)	<u>N=176</u> <u>95</u> (91-98)	<u>N=152</u> <u>99</u> (95-100)	<u>N=170</u> <u>50</u> (39-64)	<u>N=160</u> <u>124</u> (99-156)	<u>N=176</u> <u>86</u> (70- 104)	<u>N=152</u> <u>160</u> (130- 198)
<u>W-135</u>	<u>N=162</u> <u>86</u> (80-91)	<u>N=153</u> <u>99*</u> (96-100)	<u>N=162</u> <u>99</u> (96- 100)	<u>N=138</u> <u>99</u> (96-100)	<u>N=162</u> <u>55</u> (42-71)	<u>N=153</u> <u>248</u> (202- 303)	<u>N=162</u> <u>90</u> (77- 104)	<u>N=138</u> <u>244</u> (195- 305)
<u>Y</u>	<u>N=152</u> <u>67</u> (59-75)	<u>N=154</u> <u>100*</u> (98-100)	<u>N=163</u> <u>94</u> (90-97)	<u>N=146</u> <u>99</u> (96-100)	<u>N=152</u> <u>20</u> (15-26)	<u>N=154</u> <u>212</u> (175- 258)	<u>N=163</u> <u>52</u> (43-64)	<u>N=146</u> <u>254</u> (203- 318)

\* Non-inferiority criterion met (the lower limit of the two-sided 95% CI >-10 % for vaccine group differences [3-dose series minus 4-dose series].

#### 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 $\geq$ 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 (2-10 years of age)

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 $\geq$ 1:8 was demonstrated for serogroups C, W-135 and Y, but not for serogroup A. For both age groups (2 to 5 years and 6 to 10 years of age), the immune response as measured by hSBA GMTs was non-inferior for all serogroups (Table 3). In addition, the percentage of subjects with a seroresponse, percentage of subjects with hSBA $\geq$ 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 3: 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)
<b>A</b>	N=606	N=611		N=551	N=541		N=1157	N=1152	
% Seroreponse <sup>‡</sup>	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)
<b>C</b>	N=607	N=615		N=554	N=539		N=1161	N=1154	
% Seroreponse <sup>‡</sup>	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)
<b>W-135</b>	N=594	N=605		N=542	N=533		N=1136	N=1138	
% Seroreponse <sup>‡</sup>	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)
<b>Y</b>	N=593	N=600		N=545	N=539		N=1138	N=1139	
% Seroreponse <sup>‡</sup>	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)

‡ Seroreponse 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 to 10 years of age, as well as in each age strata (2 to 5 and 6 to 10 years), immune response as measured by percentage of subjects with seroreponse, 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 (Table 4). 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 4: 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/A CWY- PS)(95% CI)	Menveo (95% CI)	ACWY-PS (95% CI)	Percent Difference (Menveo – ACWY-PS) or GMT ratio (Menveo/A CWY- PS)(95% CI)
	1 month post-vaccination			12 months post-vaccination		
<b>A</b>	N=280	N=281		N=253	N=238	
Seroresponse <sup>‡</sup>	79 (74, 84)	37 (31, 43)	43* <sup>§</sup> (35,50)	n/a	n/a	
% ≥1:8	79 (74, 84)	37 (31, 43)	42* <sup>§</sup> (35, 49)	23 (18, 29)	13 (9, 18)	10 * <sup>§</sup> (3, 17)
GMT	36 (30, 44)	6.31 (5.21, 7.64)	5.74* <sup>§</sup> (4.38, 7.53)	3.88 (3.39, 4.44)	3 (2.61, 3.44)	1.29* <sup>§</sup> (1.07, 1.57)
<b>C</b>	N=281	N=283		N=252	N=240	
Seroresponse <sup>‡</sup>	64 (59, 70)	43 (38, 49)	21* <sup>§</sup> (13, 29)	n/a	n/a	
% ≥1:8	73 (68, 78)	54 (48, 60)	19* <sup>§</sup> (11, 27)	53 (47, 59)	44 (38, 51)	9* (0, 18)
GMT	26 (21, 34)	15 (12, 20)	1.71* <sup>§</sup> (1.22, 2.40)	11 (8.64, 13)	9.02 (7.23, 11)	1.19* (0.87, 1.62)
<b>W-135</b>	N=279	N=282		N=249	N=237	
Seroresponse <sup>‡</sup>	67 (61, 72)	31 (26, 37)	35* <sup>§</sup> (28, 43)	n/a	n/a	
% ≥1:8	92 (88, 95)	66 (60, 71)	26* <sup>§</sup> (20, 33)	90 (86, 94)	45 (38, 51)	46 * <sup>§</sup> (38, 53)
GMT	60 (50, 71)	14 (12, 17)	4.26* <sup>§</sup> (3.35, 5.43)	42 (35, 50)	7.57 (6.33, 9.07)	5.56* <sup>§</sup> (4.32, 7.15)
<b>Y</b>	N=280	N=282		N=250	N=239	
Seroresponse <sup>‡</sup>	75 (70, 80)	38 (32, 44)	37 * <sup>§</sup> (30, 45)	n/a	n/a	
% ≥1:8	88 (83, 91)	53 (47, 59)	34* <sup>§</sup> (27, 41)	77 (71, 82)	32 (26, 38)	45 * <sup>§</sup> (37, 53)
GMT	54 (44, 66)	11 (9.29, 14)	4.70 * <sup>§</sup> (3.49, 6.31)	27 (22, 33)	5.29 (4.34, 6.45)	5.12 * <sup>§</sup> (3.88, 6.76)

<sup>‡</sup> 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]).

<sup>§</sup> 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.

#### Persistence of immune response and booster response in children (2-10 years of age)

Persistence of immune response 1 year after primary vaccination with Menveo was

evaluated in study V59P8. 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  $\geq 1:8$  and GMTs. Menveo was non-inferior on these endpoints for serogroup C (Table 4).

Antibody persistence at 5 years after primary vaccination was assessed in the extension study V59P20E1. There was substantial antibody persistence observed against serogroups C, W and Y, with the percentages of subjects with hSBA  $\geq 1:8$  being 32% and 56% against serogroup C in subjects 2-5 and 6-10 years of age, respectively, 74% and 80% against serogroup W, and 48% and 53% against serogroup Y. GMTs were respectively 6.5 and 12 for serogroup C, 19 and 26 for serogroup W, and 8.13 and 10 for serogroup Y. For serogroup A, 14% and 22% of subjects 2-5 and 6-10 years of age, respectively, had hSBA  $\geq 1:8$  (GMTs 2.95 and 3.73). Levels for all serogroups were higher than those seen in meningococcal vaccine-naïve children of similar ages. The children also received a booster dose of Menveo, 5 years after a single dose primary vaccination. All subjects in both age groups had hSBA  $\geq 1:8$  across serogroups, with antibody titers several fold higher than seen after the primary vaccination (Table 5).

**Table 5: Persistence of immune responses 5 years after primary vaccination with Menveo, and immune responses 1 month after a booster dose among subjects aged 2 - 5 years and 6 -10 years at the time of primary vaccination**

<u>Serogroup</u>	<u>2-5 years</u>				<u>6-10 years</u>			
	<u>5 year persistence</u>		<u>1 month after booster</u>		<u>5 year persistence</u>		<u>1 month after booster</u>	
	<u>%hSBA <math>\geq 1:8</math></u> <u>(95% CI)</u>	<u>hSBA GMTs</u> <u>(95% CI)</u>	<u>%hSBA <math>\geq 1:8</math></u> <u>(95% CI)</u>	<u>hSBA GMTs</u> <u>(95% CI)</u>	<u>%hSBA <math>\geq 1:8</math></u> <u>(95% CI)</u>	<u>hSBA GMTs</u> <u>(95% CI)</u>	<u>%hSBA <math>\geq 1:8</math></u> <u>(95% CI)</u>	<u>hSBA GMTs</u> <u>(95% CI)</u>
<b><u>A</u></b>	<u>N=96</u>	<u>N=96</u>	<u>N=95</u>	<u>N=95</u>	<u>N=64</u>	<u>N=64</u>	<u>N=60</u>	<u>N=60</u>
	<u>14</u> <u>(7, 22)</u>	<u>2.95</u> <u>(2.42, 3.61)</u>	<u>100</u> <u>(96, 100)</u>	<u>361</u> <u>(299, 436)</u>	<u>22</u> <u>(13, 34)</u>	<u>3.73</u> <u>(2.74, 5.06)</u>	<u>100</u> <u>(94, 100)</u>	<u>350</u> <u>(265, 463)</u>
<b><u>C</u></b>	<u>N=96</u>	<u>N=96</u>	<u>N=94</u>	<u>N=94</u>	<u>N=64</u>	<u>N=64</u>	<u>N=60</u>	<u>N=60</u>
	<u>32</u> <u>(23, 43)</u>	<u>6.5</u> <u>(4.75, 8.9)</u>	<u>100</u> <u>(96, 100)</u>	<u>498</u> <u>(406, 610)</u>	<u>56</u> <u>(43, 69)</u>	<u>12</u> <u>(7.72, 19)</u>	<u>100</u> <u>(94, 100)</u>	<u>712</u> <u>(490, 1036)</u>
<b><u>W-135</u></b>	<u>N=96</u>	<u>N=96</u>	<u>N=95</u>	<u>N=95</u>	<u>N=64</u>	<u>N=64</u>	<u>N=60</u>	<u>N=60</u>
	<u>74</u> <u>(64, 82)</u>	<u>19</u> <u>(14, 25)</u>	<u>100</u> <u>(96, 100)</u>	<u>1534</u> <u>(1255, 1873)</u>	<u>80</u> <u>(68, 89)</u>	<u>26</u> <u>(18, 38)</u>	<u>100</u> <u>(94, 100)</u>	<u>1556</u> <u>(1083, 2237)</u>
<b><u>Y</u></b>	<u>N=96</u>	<u>N=96</u>	<u>N=94</u>	<u>N=94</u>	<u>N=64</u>	<u>N=64</u>	<u>N=59</u>	<u>N=59</u>
	<u>48</u> <u>(38, 58)</u>	<u>8.13</u> <u>(6.11, 11)</u>	<u>100</u> <u>(96, 100)</u>	<u>1693</u> <u>(1360, 2107)</u>	<u>53</u> <u>(40, 66)</u>	<u>10</u> <u>(6.51, 16)</u>	<u>100</u> <u>(94, 100)</u>	<u>1442</u> <u>(1050, 1979)</u>

#### 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 64.

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 $\geq$ 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 6).

**Table 6: 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)
<b>A</b>	N=1075	N=359		
% Seroresponse <sup>‡</sup>	75 (72, 77)	66 (61, 71)		8 (3, 14)*§
% $\geq$ 1:8	75 (73, 78)	67 (62, 72)	-	8 (3, 14)*§
GMT	29 (24, 35)	18 (14, 23)	1.63 (1.31, 2.02)*§	-
<b>C</b>	N=1396	N=460		
% Seroresponse <sup>‡</sup>	76 (73, 78)	73 (69, 77)		2 (-2, 7)*
% $\geq$ 1:8	85 (83, 87)	85 (81, 88)	-	0 (-4, 4)*
GMT	50 (39, 65)	41 (30, 55)	1.22 (0.97, 1.55)*	-
<b>W-135</b>	N=1024	N=288		
% Seroresponse <sup>‡</sup>	75 (72, 77)	63 (57, 68)		12 (6, 18)*§
% $\geq$ 1:8	96 (95, 97)	88 (84, 92)	-	8 (4, 12)*§
GMT	87 (74, 102)	44 (35, 54)	2.00 (1.66, 2.42)*§	-
<b>Y</b>	N=1036	N=294		
% Seroresponse <sup>‡</sup>	68 (65, 71)	41 (35, 47)		27 (20, 33)*§
% $\geq$ 1:8	88 (85, 90)	69 (63, 74)	-	19 (14, 25)*§
GMT	51 (42, 61)	18 (14, 23)	2.82 (2.26, 3.52)*§	-

<sup>‡</sup> Seroresponse was defined as: a) post-vaccination hSBA $\geq$ 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 $\geq$ 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 to 18 years who were seronegative at baseline (hSBA<1:4), the proportion of subjects who achieved a hSBA $\geq$ 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).

In the non-inferiority study, V59P6, immunogenicity was assessed among adolescents aged 11 to 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 $\geq$ 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 $\geq$ 1:8 (Table 7).

**Table 7: Immunogenicity of one dose of Menveo or ACWY-PS in adolescents, measured at one month post-vaccination**

Serogroup	hSBA $\geq$ 1:8 (95% CI)		hSBA GMTs (95% CI)	
	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)

#### Persistence of immune response and booster response in adolescents

In study V59P13E1, the persistence of immune responses against serogroups A, C, W-135 and Y was assessed at 21 months, 3 years and 5 years post primary vaccination among subjects aged 11-18 years at the time of vaccination.

The percentages of subjects with hSBA  $\geq$  1:8 remained constant against serogroups C, W, and Y from 21 months to 5 years postvaccination in the Menveo group and decreased slightly over time against serogroup A (Table 8). At 5 years after primary vaccination, there were significantly higher percentages of subjects with hSBA  $\geq$  1:8 in the Menveo group than in the vaccine-naïve control subjects against all the four serogroups.

**Table 8: Persistence of immune responses approximately 21 months, 3 years and 5 years after vaccination with Menveo (subjects were aged 11-18 years at the time of**

**vaccination)**

Serogroup	Timepoint	Percentages of subjects with hSBA $\geq$ 1:8			hSBA GMTs		
		Menveo (95% CI)	ACWY-D (95% CI)	P Value Menveo vs ACWY-D	Menveo (95% CI)	ACWY-D (95% CI)	P Value Menveo vs ACWY-D
<b>A</b>		N=100	N=60		N=100	N=60	
	21 months	45 (35, 55)	27 (16, 40)	0.021	6.57 (4.77-9.05)	4.10 (2.82-5.97)	0.035
	3 years	38 (28, 48)	18 (10, 30)	0.009	5.63 (3.97-7.99)	3.67 (2.44-5.53)	0.078
	5 years	35 (26, 45)	37 (25, 50)	0.83	4.43 (3.13-6.26)	4.89 (3.26-7.33)	0.68
<b>C</b>		N=100	N=59		N=100	N=59	
	21 months	61 (51, 71)	63 (49, 75)	0.83	11 (8.12-15)	7.64 (5.4-11)	0.085
	3 years	68 (58, 77)	68 (54, 79)	0.98	16 (11-25)	18 (11-29)	0.81
	5 years	64 (54, 73)	63 (49, 75)	0.87	14 (8.83-24)	20 (11-36)	0.34
<b>W-135</b>		N=99	N=57		N=99	N=57	
	21 months	86 (77, 92)	60 (46, 72)	<0.001	18 (14-25)	9.3 (6.57-13)	<0.001
	3 years	85 (76, 91)	65 (51, 77)	0.004	31 (21-46)	17 (11-28)	0.041
	5 years	85 (76, 91)	70 (57, 82)	0.029	32 (21-47)	19 (12-31)	0.074
<b>Y</b>		N=100	N=60		N=100	N=60	
	21 months	71 (61, 80)	53 (40, 66)	0.024	14 (10-19)	6.77 (4.73-9.69)	<0.001
	3 years	69 (59, 78)	55 (42, 68)	0.075	14 (9.68-20)	7.11 (4.65-11)	0.008
	5 years	67 (57, 76)	55 (42, 68)	0.13	13 (8.8-20)	8.02 (4.94-13)	0.078

A booster dose of Menveo was administered 3 years after primary vaccination with Menveo or ACWY-D. Both groups showed a robust response to the booster dose of Menveo at one month after vaccination (100% of subjects had hSBA  $\geq$  1:8 across serogroups) and this response largely persisted through 2 years after the booster dose for serogroups C, W and Y (with 87% to 100% of subjects with hSBA  $\geq$  1:8 across serogroups). A small decline was observed in percentages of subjects with hSBA  $\geq$  1:8 against serogroup A, although percentages were still high (77% to 79%).

GMTs declined over time as expected but remained between 2- and 8-fold higher than

prebooster values (Table 8).

In study V59P6E1, at one year post vaccination, the percentage of Menveo recipients with hSBA  $\geq 1:8$  remained significantly 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. In 5 years post vaccination, the percentage of Menveo recipients with hSBA  $\geq 1:8$  remained significantly higher compared with ACWY-PS recipients for serogroups C and Y. Higher hSBA GMTs were observed for serogroups W-135 and Y (Table 9).

**Table 9: Persistence of immune responses approximately 12 months and 5 years after vaccination with Menveo and ACWY-PS (subjects were aged 11-18 years at the time of vaccination)**

Serogroup	Timepoint	Percentages of subjects with hSBA $\geq 1:8$			hSBA GMTs		
		Menveo	ACWY-PS	P Value Menveo vs ACWY-PS	Menveo	ACWY-PS	P Value Menveo vs ACWY-PS
A		N=50	N=50		N=50	N=50	
	12 months	41% (27, 56)	43% (28, 59)	0.73	5.19 (3.34, 8.09)	6.19 (3.96, 9.66)	0.54
	5 years	30% (18, 45)	44% (30, 59)	0.15	5.38 (3.29, 8.78)	7.75 (4.83, 12)	0.24
C		N=50	N=50		N=50	N=50	
	12 months	82% (68, 91)	52% (37, 68)	<0.001	29 (15, 57)	17 (8.55, 33)	0.22
	5 years	76% (62, 87)	62% (47, 75)	0.042	21 (12, 37)	20 (12, 35)	0.92
W-135		N=50	N=50		N=50	N=50	
	12 months	92% (80, 98)	52% (37, 68)	<0.001	41 (26, 64)	10 (6.41, 16)	<0.001
	5 years	72% (58, 84)	56% (41, 70)	0.093	30 (18, 52)	13 (7.65, 22)	0.012
Y		N=50	N=50		N=50	N=50	
	12 months	78% (63, 88)	50% (35, 65)	0.001	34 (20, 57)	9.28 (5.5, 16)	<0.001
	5 years	76% (62, 87)	50% (36, 64)	0.002	30 (18, 49)	8.25 (5.03, 14)	<0.001

A booster dose of Menveo was administered 5 years after primary vaccination with Menveo or ACWY-PS. At 7 days after the booster dose, 98%-100% of subjects who previously received Menveo and 73%-84% of subjects who previously received ACWY-PS achieved hSBA  $\geq 1:8$  against serogroups A, C, W-135 and Y. At one month post vaccination, the percentages of subjects with hSBA $\geq 1:8$  were 98%-100% and 84%-96%, respectively.

A significant increase in the hSBA GMTs against all four serogroups was also observed at 7 and 28 days after the booster dose (Table 10).

**Table 10: Response to Booster: bactericidal antibody responses to Menveo booster administered at 3 or 5 years after the primary vaccination with Menveo or ACWY-D or ACWY-PS in subjects aged 11-17 years**

Serogroup	Time point	Percentages of subjects with hSBA $\geq$ 1:8				hSBA GMTs			
		V59P13E1 (3 years post vaccination)		V59P6E1 (5 years post vaccination)		V59P13E1 (3 years post vaccination)		V59P6E1 (5 years post vaccination)	
		Menveo	ACWY-D	Menveo	ACWY-PS	Menveo	ACWY-D	Menveo	ACWY-PS
<b>A</b>		N=42	N=30	N=49	N=49	N=42	N=30	N=49	N=49
	Pre-booster	21% (10, 37)	20% (8, 39)	29% (17, 43)	43% (29, 58)	2.69 (1.68, 4.31)	2.81 (1.68, 4.69)	5.16 (3.46, 7.7)	7.31 (4.94, 11)
	7 days	-	-	100% (93, 100)	73% (59, 85)	-	-	1059 (585, 1917)	45 (25, 80)
	28 days	100% (92, 100)	100% (88, 100)	98% (89, 100)	94% (83, 99)	326 (215, 494)	390 (248, 614)	819 (514, 1305)	147 (94, 232)
	2 years	79% (63, 90)	77% (58, 90)	-	-	22 (12, 41)	20 (10, 39)	-	-
<b>C</b>		N=42	N=30	N=49	N=49	N=42	N=30	N=49	N=49
	Pre-booster	55% (39, 70)	60% (41, 77)	78% (63, 88)	61% (46, 75)	16 (8.66, 31)	15 (7.46, 30)	20 (13, 33)	19 (12, 31)
	7 days	-	-	100% (93, 100)	78% (63, 88)	-	-	1603 (893, 2877)	36 (20, 64)
	28 days	100% (92, 100)	100% (88, 100)	100% (93, 100)	84% (70, 93)	597 (352, 1014)	477 (268, 849)	1217 (717, 2066)	51 (30, 86)
	2 years	95% (84-99)	87% (69-96)	-	-	124 (62-250)	61 (29-132)	-	-
<b>W-135</b>		N=41	N=29	N=49	N=49	N=41	N=29	N=49	N=49
	Pre-booster	88% (74, 96)	83% (64, 94)	73% (59, 85)	55% (40, 69)	37 (21, 65)	21 (11, 38)	29 (17, 49)	12 (7.02, 19)
	7 days	-	-	100% (93, 100)	84% (70, 93)	-	-	1685 (1042, 2725)	34 (21, 54)

				100)					
	28 days	100 % (91, 100)	100% (88, 100)	100 % (93, 100)	92% (80, 98)	673 (398, 1137)	1111 (631, 1956)	1644 (1090, 2481)	47 (32, 71)
	2 years	100 % (91, 100)	97% (82, 100)	-	-	93 (58, 148)	110 (67, 183)	-	
<b>Y</b>		N=42	N=30	N=49	N=49	N=42	N=30	N=49	N=49
	Pre-booster	74% (58, 86)	53% (34, 72)	78% (63, 88)	51% (36, 66)	14 (8.15, 26)	8.9 (4.76, 17)	28 (18, 45)	7.8 (4.91, 12)
	7 days	-	-	98% (89, 100)	76% (61, 87)	-	-	2561 (1526, 4298)	21 (13, 35)
	28 days	100 % (92, 100)	100% (88, 100)	100 % (93, 100)	96% (86, 100)	532 (300, 942)	454 (243, 846)	2092 (1340, 3268)	63 (41, 98)
	2 years	95% (84, 99)	93% (78, 99)	-	-	55 (30, 101)	46 (24, 89)	-	-

### 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 11. Non-inferiority of Menveo to ACWY-D was demonstrated for all four serogroups using the primary endpoint (hSBA seroresponse) (Table 11).

**Table 11: Serum bactericidal antibody responses following Menveo one month after vaccination among subjects aged 19 to 55 years**

Endpoint by Serogroup	Menveo (95% CI)	ACWY-D (95% CI)	Menveo /ACWY-D (95% CI)	Menveo minus ACWY-D (95% CI)
<b>A</b>	N=963	N=321		
% Seroresponse <sup>‡</sup>	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)*	-
<b>C</b>	N=902	N=300		
% Seroresponse <sup>‡</sup>	68 (64, 71)	60 (54, 65)		8 (2, 14)* <sup>§</sup>
% ≥1:8	80 (77, 83)	74 (69, 79)	-	6 (1, 12)* <sup>§</sup>
GMT	50 (43, 59)	34 (26, 43)	1.50 (1.14, 1.97)* <sup>§</sup>	-
<b>W-135</b>	N=484	N=292		
% Seroresponse <sup>‡</sup>	50 (46, 55)	41 (35, 47)		9 (2, 17)* <sup>§</sup>
% ≥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 <sup>‡</sup>	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)* §	-

<sup>‡</sup> 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 to 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).

The onset of immune response after the primary vaccination with Menveo in healthy subjects 18 through 22 years of age was evaluated in study V59P6E1. At 7 days post vaccination, 64% of subjects achieved hSBA ≥1:8 against serogroup A and 88% through 90% of subjects had bactericidal antibodies against serogroups C, W-135 and Y. At one month post vaccination, 92% through 98% of subjects had hSBA ≥1:8 against serogroups A, C, W-135 and Y. A robust immune response as measured by hSBA GMTs against all serogroups was also observed at 7 days (GMTs 34 through 70) and 28 days (GMTs 79 through 127) after a single dose vaccination.

#### Immunogenicity in older adults

The comparative immunogenicity of Menveo vs. ACWY-PS was evaluated in subjects aged 56 to 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 12: Immunogenicity of one dose of Menveo or ACWY-PS in adults aged 56 to 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 (butyl 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**

GlaxoSmithKline Pte Ltd  
23 Rochester Park, Singapore 139234

**Version:** GDS10(b) (SI)

**Revision date:** 09 Aug 2019

[GSK logo]