MENVEO®

Meningococcal Group A, C W135 and Y Conjugate Vaccine

1. NAME OF THE MEDICINAL PRODUCT

Menveo powder and solution for solution for injection
Meningococcal Group A, C, W135 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 W135 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 (powder and 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 years of age) and adults at risk of exposure to *Neisseria meningitidis* groups A, C, W135 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

Adults and children (above 5 years of age)
Menveo should be administered as a single 0.5 ml injection.

Children (2-5 years of age)
Menveo should be administered as a single 0.5 ml injection. A second dose may be administered 2 months after the first dose.

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

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

Method of administration
Menveo is given as an intramuscular injection, preferably into the deltoid muscle.
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 substance or to any of the excipients, including diphtheria toxoid (CRM_{197}), or a life-threatening reaction after previous administration of a vaccine containing similar components (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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.

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.

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 vaccines (see section PHARMACODYNAMIC PROPERTIES).

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, W135 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.

4.5 Interaction with other medicinal products and other forms of interaction

For children 2 to 10 years of age, no data are available for evaluating safety and immunogenicity of other childhood vaccines when administered concomitantly with Menveo.

Menveo has been evaluated in two co-administration studies with either Tetanus, Reduced Diphtheria and Acellular Pertussis Vaccine, Adsorbed (Tdap) alone or Tdap and Human Papillomavirus Quadrivalent (Types 6, 11, 16 and 18) Vaccine, Recombinant (HPV), both of which support the co-administration of the vaccines.

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 or HPV vaccine components were not negatively affected by co-administration.

The administration of Menveo one month after Tdap resulted in statistically significantly lower group W135 seroresponses. Since there was no direct impact on the seroprotection rate, the clinical consequences are presently unknown.

There was evidence of some suppression of antibody response to two of the three pertussis antigens. The clinical relevance of this observation is unknown. After vaccination, over 97% of subjects had detectable pertussis titers to all three pertussis antigens.

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. It should be checked if the adverse reactions may be intensified by any co-administration.

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

4.6 Fertility, pregnancy and lactation

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 and Y, pregnancy should not preclude vaccination when the risk of exposure is clearly defined.

Although insufficient clinical data on the use of Menveo during breast-feeding are available, it is unlikely that secreted antibodies in milk would be harmful when ingested by a breastfed infant. Therefore, Menveo may be used during breast feeding.

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

Within each frequency grouping, adverse reactions are presented in the 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 to10 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 disorders

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 6,401 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.

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

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

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.

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 children (2-10 years of age), adolescents (11-18 years of age) adults (19-55 years of age) and older adults (56-65 years of age).

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 1). 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 1: 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)**	**Menevo (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 the same study, separate group of children, 2 through 5 years of age (N=297) in the per protocol population) were immunized with two doses of Menveo, two months apart. The observed seroresponse rates (with 95% CI) at 1 month after the second dose were: 91% (87-94), 98% (95-99), 89% (85-92), and 95% (91-97) for serogroups A, C, W-135 and Y, respectively. The proportion of subjects with hSBA ≥ 1:8 (95% CI) was 91% (88-94), 99% (97-100), 99% (98-100), and 98% (95-99) for serogroups A, C, W-135 and Y, respectively. The hSBA GMTs (95% CI) for this group were 64 (51-81), 144 (118-177), 132 (111-157), and 102 (82-126) for serogroups A, C, W-135 and Y, respectively.

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 2).

Table 2: 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 individuals 11 years of age and above

In the pivotal study (V59P13), participants received either a dose of Menveo (N = 2649) or comparator vaccine (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.

Immunogenicity in adolescents

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 3.

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 and with hSBA ≥ 1:8 were statistically higher for serogroups A, W-135, and Y in the Menveo group, as compared to the ACWY-D group, while the ratio of GMTs for

Menveo vs. ACWY-D was statistically higher for all four serogroups (Table 3). The clinical relevance of higher post-vaccination immune responses is unknown.

Table 3: 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 hSB ≥ 1:8 after a dose of Menveo were as follows: serogroup A 75% (780/1039); serogroup C 80% (735/923); serogroup W135 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 4.

Table 4: 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)	Menveo vs ACWY-D (95% CI)	Menveo vs Naive (95% CI)	ACWY-D vs Naive (95% CI)
A	N=275	N=179	N=97	**P-value§**	**P-value§**	**P-value§**
% ≥1:8	36 (30, 42)	23 (17, 30)	5 (2, 12)	0.040*	0.012*	0.012*
GMT	5.29 (4.63, 6.05)	3.5 (2.97, 4.14)	2.36 (1.88, 2.96)	0.012*	0.012*	0.030*
C	N=275	N=179	N=97			
% ≥1:8	62 (56, 68)	59 (52, 66)	42 (32, 53)	0.360	0.012*	0.040*
GMT	10 (9.02, 12)	8.96 (7.51, 11)	5.95 (4.68, 7.56)	0.200	0.012*	0.028*
W-135	N=273	N=176	N=97			
% ≥1:8	84 (79, 88)	74 (67, 80)	51 (40, 61)	0.036*	0.012*	0.012*
GMT	18 (15, 20)	14 (12, 17)	7.80 (6.11, 9.97)	0.154	0.012*	0.012*
Y	N=275	179	N=97			
% ≥1:8	67 (61, 72)	54 (47, 62)	40 (30, 51)	0.040*	0.012*	0.046*
GMT	12 (10, 14)	7.85 (6.54, 9.43)	5.14 (4.01, 6.60)	0.012*	0.012*	0.028*

‡ Age matched subjects not previously immunized with meningococcal vaccine
§ Adjusted for multiple comparisons using step-down Bonferroni (Holm) method
* P-value < 0.05

In the non-inferiority study, V59P6, immunogenicity was assessed among adolescents aged 11-17 years who had been randomized to receive either Menveo or 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 5).

Table 5: Immunogenicity of one dose of Menveo or ACWY-PS in adolescents, measured at one month post vaccination

Endpoint by Serogroup	Menveo (95% CI)	ACWY-PS (95% CI)	Menveo minus ACWY-PS+ (95% CI)	Menveo/ACWY-PS† (95% CI)
A	N=148	N=179		
% Seroresponse‡	80 (73, 86)	41 (34, 49)	39* § (29, 48)	

% ≥ 1:8	81 (74, 87)	41 (34, 49)	40* § (30, 49)	
GMT	34 (26, 44)	6.97 (5.51, 8.82)	-	4.87* § (3.41, 6.95)
C	N=148	N=177		
% Seroresponse‡	76 (68, 82)	54 (47, 62)	21* § (11, 31)	
% ≥ 1:8	83 (76, 89)	63 (56, 70)	20 (10, 29)* §	
GMT	58 (39, 85)	30 (21, 43)	-	1.9* § (1.13, 3.19)
W-135	N=146	N=173		
% Seroresponse‡	84 (77, 90)	71 (63, 77)	14* § (5, 23)	
% ≥ 1:8	90 (84, 95)	86 (80, 91)	4* (-3, 11)	
GMT	49 (39, 62)	30 (24, 37)	-	1.65* § (1.22, 2.24)
Y	N=147	N=177		
% Seroresponse‡	86 (79, 91)	66 (59, 73)	20* § (11, 28)	
% ≥ 1:8	95 (90, 98)	81% (74, 86)	14* § (7, 21)	
GMT	100 (74, 134)	34 (26, 45)	-	2.91* § (1.99, 4.27)

‡ 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.
+Difference in proportions for Menveo minus ACWY-PS
† Ratio of GMTs for Menveo to ACWY-PS.
* Non inferiority criterion met (the lower limit of the two-sided 95% CI >-10 % for vaccine group differences[Menveo minus ACWY-PS], >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.

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 6. Non-inferiority of Menveo to ACWY-D was demonstrated for all four serogroups using the primary endpoint (hSBA seroresponse) (Table 6). Both hSBA GMTs and the percentage of subjects with hSBA seroresponse were statistically higher for serogroups C, W-135,

and Y among Menveo recipients than in ACWY-D recipients. The percentage of subjects wit hSBA ≥ 1:8 was statistically higher for serogroups C and Y among Menveo recipients, as compared to the corresponding groups in ACWY-D recipients (Table 6). The clinical relevance of higher post-vaccination immune responses is not known.

Table 6: 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 W135 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 for all endpoints (seroresponse, hSBA ≥ 1:8, and GMT). In addition, statistically higher responses among Menveo recipients were observed for serogroup C GMTs (Table 7).

Table 7: Immunogenicity of one dose of Menveo or ACWY-PS in adults aged 56-65 years, measured at one month post vaccination.

Endpoint by Serogroup	Menveo (95% CI)	ACWY-PS (95% CI)	Menveo/ ACWY-PS (95% CI)	Menveo minus ACWY-PS (95% CI)
A	N=83	N=41		
% Seroresponse‡	86% (76, 92)	61% (45,76)	-	25 (9, 41)* §
% hSBA ≥ 1:8	87 (78, 93)	63 (47, 78)	-	23 (8, 40)* §
GMT	111 (70,175)	21 (11,39)	5.4 (2.47, 12)* §	-
C	N=84	N=41		
% Seroresponse‡	83% (74, 91)	73% (57, 86)	-	10 (-4, 27)*
% hSBA ≥ 1:8	90 (82, 96)	83 (68, 93)	-	8 (-4, 23)*
GMT	196 (125,306)	86 (45,163)	2.27 (1.05, 4.95)* §	-
W-135	N=82	N=39		
% Seroresponse‡	61% (50, 72)	54% (37,70)	-	7 (-11, 26)
% hSBA ≥ 1:8	94 (86, 98)	95 (83, 99)	-	-1 (-9, 11)*
GMT	164 (112,240)	132 (76,229)	1.24 (0.64, 2.42)*	-
Y	N=84	N=41		
% Seroresponse‡	77% (67, 86)	54% (37,69)	-	24 (6, 41)* §

% hSBA ≥ 1:8	88 (79, 94)	68 (52, 82)	-	20 (5, 36)* §
GMT	121 (76,193)	28 (15,55)	4.25 (1.89, 9.56)* §	-

‡ 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.

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
Powder
Sucrose
Potassium dihydrogen phosphate

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

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section SPECIAL PRECAUTIONS FOR DISPOSAL AND HANDLING.

6.3 Shelf life
3 years.

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 vial(s) and/or syringe 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

Vial-Syringe presentation

Powder in vial (type I glass) with a stopper (halobutyl rubber) and solution in pre-filled syringe (type I glass) with a tip cap (type I elastomeric closure with natural rubber latex or type II elastomeric closure that has no detectable natural rubber latex.

Each pack contains a single dose of one vial and one pre-filled syringe.

Vial-Vial presentation

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.

Vial-Syringe presentation:

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

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

Remove the tip cap from the syringe and attach a suitable needle for the withdrawal (21G, 1 ½ inch length or a 21G, 40 mm length). Use the whole contents of the syringe (0.6 ml) to reconstitute the powder.

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.

Vial-Vial presentation:

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 a 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.

For all presentations:
Previously frozen product should not be used. For a description on use, see section SHELF LIFE.

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

7. MARKETING AUTHORISATION HOLDER

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8. DATE OF REVISION OF THE TEXT

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