MENVEO

Powder and solution for injection
Meningococcal Group A, C, W135 and Y conjugate vaccine

QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 mL of the reconstituted vaccine) contains:
Each powder vial contains:

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

Each solution vial contains:

• 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 "*List of Excipients*".

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.

CLINICAL PARTICULARS

Indications

Menveo is indicated for active immunization of travellers to endemic area in children (from 7 months of age), adolescent and adults at risk of exposure to *Neisseria meningitidis* serogroup A, C, W135, and Y to prevent invasive disease.

The use of this vaccine should be in accordance with official recommendations.

Dosage and Administration

Dosing in different populations:

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

Vaccine schedule for children 2 to 10 years of age
Menveo is to be administered intramuscularly as a single dose (0.5 mL) injection. For children 2 through 5 years of age at continued high risk of meningococcal disease a second dose may be administered 2 months after the first dose. The duration of protection following immunization is not known.

Vaccine schedule for adolescents and adults (from 11 years of age)
Menveo is to be administered as single dose (0.5 mL).

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

Geriatric population
There are no data in individuals older than 65 years of age.

There are limited data in individuals aged 56-65 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 "*Special Precautions for Disposal and Other Handling*".

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

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 vaccinees (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.

Interaction
Several clinical trials involving children 7 to 23 months, studied concomitant use of ***Menveo*** with 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 MMRV. No increase in the reactogenicity or change in the safety profile of the routine vaccines was observed. In a clinical trial of children ≥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.

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***.

In the adolescents (11 to 18 years of age), ***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 serogroup 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.

Pregnancy and Breast-feeding
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, W135 and Y, pregnancy should not preclude vaccination when the risk of exposure is clearly defined.

Breast-feeding
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.

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.

Adverse Reactions
Adverse reactions from clinical trials
Adverse reactions from clinical trials
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 7 to 23 months of age
The safety of ***Menveo*** with 2-dose schedule was assessed in 2,180 children immunized between 6 and 23 months of age was evaluated in four randomized studies that addressed the safety of ***Menveo*** administered concomitantly with routine paediatric vaccines.

In three studies, the safety of one dose of ***Menveo*** when given concomitantly with routine paediatric vaccines in the second year of life was evaluated in 537 subjects. The rates of solicited adverse events reported were comparable between ***Menveo*** and MenC conjugate vaccine.

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 : diarrhoea, vomiting

Skin and subcutaneous tissue disorders:
Common : rash

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

Children 2 to 10 years of age
The safety of ***Menveo*** in children 2 to 10 years of age was evaluated in 4 clinical trials in which 3,181 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, diarrhoea

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 (>50 mm), injection site induration (>50 mm), chills, fever ≥38°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 6,185 participants (from 11-65 years) who received ***Menveo***. Among ***Menveo*** recipients, 61%, 17%, 22% 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=2,663) and 19 to 55 years (N=1,606), respectively.

The incidence and severity of any, local, systemic, and other reactions were generally similar in the ***Menveo*** groups across all studies and within the adolescent and adult age groups. The reactogenicity

profile and rates of adverse events among subjects aged 56-65 years who received ***Menveo*** (N=216), were similar to that observed in ***Menveo*** recipients subjects aged 11-55 years.

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

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

Nervous system disorders:
Very common : headache
Uncommon : dizziness

Gastrointestinal disorders:
Very common : nausea

Skin and subcutaneous tissue disorders:
Common : rash

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.

Overdose
No case of overdose has been reported.

Clinical Pharmacology
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 6 months through 65 years of age.

Immune responses following a 2-dose series in children 6 months through 23 months of age.
The immunogenicity of ***Menveo*** was assessed in children, who did not receive the 4-dose series but instead received 2 dose series. Among the per protocol population of 386 subjects, after ***Menveo*** administered at 7-9 and at 12 months, the proportions of subjects with hSBA ≥1:8 for serogroups A, C, W-135, and Y were respectively: 88% (84-91), 100% (98-100), 98% (96-100), 96% (93-99).

A 2-dose series was also examined in a study of Latin American children, who received ***Menveo*** at 12 and 16 months of age. Among the per protocol population of 106 subjects, the proportions of subjects with hSBA ≥1:8 for serogroups A, C, W-135 and Y were 97% (92-99), 100% (96-100), 100% (96-100), and 100% (96-100), respectively.

Immunogenicity in children
In the pivotal study V59P20 immunogenicity of ***Menveo*** was compared to ACWY-D; 1,170 children were vaccinated with ***Menveo*** and 1,161 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)**	***Menveo* (95% CI)**	**ACWY-D (95% CI)**	**Percent Difference (*Menveo* – ACWY-D) or GMT ratio (*Menveo*/ ACWY-D) (95% CI)**
A	N= 606	N= 611		N= 551	N= 541		N= 1,157	N= 1,152	
% 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= 1,161	N= 1,154	
% 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= 1,136	N= 1,138	
% 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= 1,138	N= 1,139	
% 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) were 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= 2,649) or quadrivalent, diphtheria toxoid conjugated, meningococcal vaccine as comparator (ACWY-D) (N= 875). Sera were obtained both before vaccination and 28 days 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*** or ACWY-D are summarized below in Table 3.

In the subset of subjects aged 11-18 years who were seronegative at baseline (hSBA <1:4), the proportion of subjects who achieved a titer ≥1:8 after a dose of ***Menveo*** were as follows: serogroup A 75% (780/1,039); serogroup C 79% (771/977); serogroup W-135 94% (570/609); serogroup Y 81% (510/630).

Table 3: Serum bactericidal antibody responses following *Menveo* one month after vaccination among subjects aged 11-18 years

Serogroup	N	GMT (95% CI)	hSBA ≥1:8 (95% CI)
A	1,075	29 (24, 35)	75% (73, 78)
C	1,483	59 (48, 73)	84% (82, 86)
W-135	1,024	87 (74, 102)	96% (95, 97)

Y	1,036	51 (42, 61)	88% (85, 90)

The persistence of immune responses for ***Menveo*** at 21 months post-vaccination among subjects aged 11-18 years at the time of vaccination is shown in the Table 4.

Table 4: Persistence of immune responses approximately 21 months after vaccination with *Menveo* (subjects were aged 11-18 years at vaccination)

Serogroup	GMT (95% CI)	hSBA ≥1:8 (95% CI)
A	5.29 (4.63, 6.05)	36% (30, 42)
C	10 (9.02, 12)	62% (56, 68)
W-135	18 (15, 20)	84% (79, 88)
Y	12 (10, 14)	67% (61, 72)

In the non-inferiority study, V59P6, immunogenicity was assessed among adolescents aged 11-17 years who had been randomized to receive either ***Menveo*** or quadrivalent meningococcal polysaccharide vaccine (ACWY-PS). ***Menveo*** was shown to be non-inferior to ACWY-PS vaccine for all four serogroups (A, C, W and Y) based on seroresponse, proportions achieving hSBA titres ≥1:8, and GMTs,

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

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

At one year post-vaccination in these same subjects, compared with ACWY-PS, a higher proportion of subjects vaccinated with ***Menveo*** had hSBA titers ≥1:8 for serogroups C, W, and Y, with comparable levels 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. In the subset of subjects aged 19-55 years who were seronegative at baseline, the proportion of subjects who achieved a titer ≥1:8 after a dose of ***Menveo*** were as follows: serogroup A 67% (582/875); serogroup C 71% (425/596); serogroup W-135 82% (131/160); serogroup Y 66% (173/263).

Table 6: Serum bactericidal antibody responses following *Menveo* one month after vaccination among subjects aged 19-55 years

Serogroup	N	GMT (95% CI)	hSBA ≥1:8 (95% CI)
A	963	31 (27, 36)	69% (66, 72)
C	961	52 (44, 60)	80% (77, 83)
W-135	484	111 (93, 132)	94% (91, 96)
Y	503	44 (37, 52)	79% (76, 83)

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 titers ≥1:8 was non-inferior to ACWY-PS for all four serogroups and statistically superior for serogroups A and Y.

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

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

Pharmacokinetic Properties
Not applicable.

Pre-clinical 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 post natal day 29.

No effects on fertility were observed in female rabbits receiving ***Menveo*** pre-mating and during pregnancy.

PHARMACEUTICAL PARTICULARS
List of Excipients
Powder
Sucrose
Potassium dihydrogen phosphate

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

Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section "*Special Precautions for Disposal and Other Handling*".

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.

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 "*Shelf Life*".

Nature and Contents of Container
Vial-Vial presentation

- Powder for 1 dose in a vial (type I glass) with a stopper (butyl rubber)
- Solution for 1 dose in a vial (type I glass) with a stopper (butyl rubber).

Pack size of one dose: 1 vial of powder plus 1 vial of solution or pack size of 5 doses: 5 vials of powder plus 5 vials of solution.

Special Precautions for Disposal and Other Handling
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.

Package
Box, 1 dose (2 vials) Reg. No. XXXXXXXXXXXXXX
Each dose contains of 1 vial of powder for injection MenA Lyophilized Conjugate Component + 1 vial @ 0.6 mL solution for injection MenCWY Liquid Conjugate Component.

Box, 5 doses (10 vials) Reg. No. XXXXXXXXXXXXXX
Each dose contains of 1 vial of powder for injection MenA Lyophilized Conjugate Component + 1 vial @ 0.6 mL solution for injection MenCWY Liquid Conjugate Component.

HARUS DENGAN RESEP DOKTER

Manufactured by
GSK Vaccines S.r.l. – Bellaria – Rosia, Siena, Italy
For GSK Vaccines S.r.l, Via Fiorentina, Siena, Italy

Imported by
PT Glaxo Wellcome Indonesia
Jakarta, Indonesia

Version Number: 008 – MA Transfer SBP to GWI (RINJANI) / Date of issue: 5 December 2018

PACKAGE LEAFLET: INFORMASI UNTUK PASIEN

Menveo, serbuk dan larutan untuk injeksi

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

Baca Leaflet Ini Dengan Saksama Sebelum Anda atau Anak Anda Mendapatkan Vaksin Ini.
- Simpan leaflet ini. Anda mungkin butuh untuk membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, Anda dapat menghubungi dokter atau apoteker Anda.
- Vaksin ini diresepkan untuk Anda atau anak Anda. Jangan diberikan untuk orang lain.
- Jika ada kejadian ikutan pasca imunisasi (KIPI) yang menjadi serius atau jika Anda mengalami KIPI yang tidak tercantum pada leaflet ini, harap hubungi dokter atau apoteker Anda.

Pada Leaflet Ini:

1. Apakah *Menveo* Itu dan Digunakan untuk Apa

Menveo adalah vaksin untuk digunakan pada anak-anak (dari usia 7 bulan), remaja dan dewasa untuk mencegah penyakit invasif yang disebabkan oleh bakteri yang disebut *Neisseria meningitidis* kelompok A, C W-135 dan Y.

Bakteri ini dapat menyebabkan infeksi serius dan terkadang mengancam jiwa seperti meningitis dan sepsis (keracunan darah).

Menveo membantu tubuh Anda membuat perlindungan sendiri (antibodi) terhadap penyakit ini. Vaksin ini tidak dapat menyebabkan penyakit meningitis.

Seperti semua vaksin, ***Menveo*** mungkin tidak sepenuhnya melindungi semua orang yang divaksinasi.

Menveo hanya akan melindungi terhadap penyakit yang disebabkan oleh empat kelompok *Neisseria meningitidis* yang terkandung dalam vaksin ini. Vaksin ini tidak akan melindungi terhadap infeksi yang disebabkan oleh kelompok lain dari *Neisseria meningitidis*.

2. Apa yang Perlu Anda Ketahui Sebelum Mendapatkan *Menveo*

Menveo tidak boleh diberikan:
- Jika Anda atau anak Anda memiliki reaksi alergi (hipersensitif) terhadap ***Menveo,*** atau bahan lain yang terkandung dalam ***Menveo*** (tercantum pada *Bagian 5*), termasuk *diphteria toxoid*. Tanda-tanda reaksi alergi dapat meliputi gatal pada ruam kulit, sesak napas, dan pembengkakan pada wajah atau lidah.

Konsultasikan dengan dokter Anda jika Anda atau anak Anda mengalami salah satu dari tanda tersebut di atas.

Peringatan dan tindakan pencegahan

Dokter Anda perlu mengetahui hal-hal berikut sebelum Anda atau anak Anda mendapatkan ***Menveo***:
- Jika Anda atau anak Anda mengalami infeksi berat dengan demam tinggi. Pada kasus ini, vaksinasi dapat ditunda sampai keadaan membaik. Infeksi ringan seperti pilek seharusnya tidak menjadi masalah, namun demikian konsultasikan dengan dokter Anda terlebih dahulu.
- Jika Anda atau anak Anda memiliki sistem kekebalan tubuh yang lemah. Ada kemungkinan bahwa efektivitas ***Menveo*** dapat berkurang.
- Jika Anda menerima pengobatan yang menghalangi bagian dari sistem kekebalan yang dikenal sebagai *complement activation*. Bahkan jika Anda telah divaksinasi dengan ***Menveo***, Anda tetap berisiko tinggi terkena penyakit yang disebabkan oleh bakteri *Neisseria meningitidis* kelompok A, C, W-135 dan Y.

Pingsan dapat terjadi setelah, atau bahkan sebelum suntikan, oleh karena itu beri tahu dokter atau perawat jika Anda atau anak Anda pingsan pada penyuntikan sebelumnya.

Penggunaan obat atau vaksin lain
Beri tahu dokter atau apoteker Anda jika Anda atau anak Anda sedang atau baru saja menggunakan obat lain, termasuk obat yang didapatkan tanpa resep atau vaksin lain.

Menveo dapat diberikan bersamaan dengan vaksin lain dengan tempat suntikan yang berbeda untuk setiap jenis vaksin.

Kehamilan dan menyusui
Konsultasikan dengan dokter atau apoteker Anda sebelum menggunakan obat apa pun.

Mengemudi dan menggunakan mesin
Tidak ada informasi apakah ***Menveo*** mempengaruhi kemampuan mengemudi atau menggunakan mesin. Namun, jangan mengemudi atau menggunakan mesin jika Anda merasa tidak sehat.

3. Bagaimana Cara Pemberian *Menveo*

Menveo (0.5 mL) akan diberikan oleh dokter atau perawat.
Anda akan diberi tahu jika Anda atau anak Anda harus kembali untuk dosis ***Menveo*** selanjutnya.

Menveo akan disuntikan ke dalam otot, biasanya di paha untuk bayi atau lengan atas untuk anak-anak, remaja dan dewasa.

Anak-anak yang tidak divaksinasi dari usia 7 hingga 23 bulan:
Dua suntikan, dengan suntikan kedua diberikan pada tahun kedua kehidupan dan setidaknya 2 bulan setelah suntikan pertama.

Anak-anak di atas usia 2 tahun, remaja dan dewasa:
Satu suntikan.

Harap beri tahu dokter Anda jika Anda atau anak Anda telah menerima suntikan ***Menveo*** atau vaksin meningokokus lainnya.

Dokter Anda akan memberi tahu Anda jika Anda memerlukan suntikan ***Menveo*** tambahan.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan vaksin ini, tanyakan kepada dokter atau perawat Anda.

Jika Anda melewatkan satu dosis *Menveo*
Jika anak Anda melewatkan jadwal suntikan yang sudah ditentukan, Anda harus menjadwalkan waktu lain untuk kunjungan dengan dokter.

Pastikan anak Anda menyelesaikan vaksinasi lengkap. Jika tidak, anak Anda mungkin tidak sepenuhnya terlindungi.

4. Kemungkinan Kejadian Ikutan Pasca Imunisasi (KIPI)

Seperti obat-obatan lain, ***Menveo*** dapat menyebabkan KIPI, walaupun tidak semua orang akan mengalami KIPI.

Anak-anak dari usia 7 hingga 23 bulan:

Sangat umum (ini dapat terjadi lebih dari 1 dalam 10 dosis vaksin):
- Perubahan kebiasaan makan
- Menangis terus-menerus
- Mengantuk
- Diare
- Muntah
- Mudah marah
- Nyeri pada tempat suntikan
- Kemerahan pada tempat suntikan (≤50 mm)
- Indurasi (pengerasan kulit) pada tempat suntikan (≤50 mm).

Umum (ini dapat terjadi hingga 1 dari 10 dosis vaksin):
- Ruam
- Nyeri parah pada tempat suntikan
- Demam.

Tidak umum (ini dapat terjadi hingga 1 dari 100 dosis vaksin)
- Kemerahan pada tempat suntikan (>50 mm)
- Indurasi (pengerasan kulit) pada tempat suntikan (>50 mm).

Anak-anak dari usia 2 hingga 10 tahun:

Sangat umum (ini dapat terjadi lebih dari 1 dalam 10 dosis vaksin):
- Mengantuk
- Sakit kepala
- Mudah marah
- Merasa tidak nyaman
- Nyeri pada tempat suntikan
- Kemerahan pada tempat suntikan (≤50 mm)
- Indurasi (pengerasan kulit) pada tempat suntikan (≤50 mm).

Umum (ini dapat terjadi hingga 1 dari 10 dosis vaksin):
- Perubahan kebiasaan makan
- Mual
- Muntah
- Diare
- Ruam
- Sakit otot
- Nyeri sendi
- Kedinginan
- Demam (≥38°C)
- Kemerahan pada tempat suntikan (>50 mm)
- Indurasi (pengerasan kulit) pada tempat suntikan (>50 mm).

Tidak umum (ini dapat terjadi hingga 1 dari 100 dosis vaksin)
- Gatal pada tempat suntikan.

Remaja (dari usia 11 tahun) dan dewasa:

Sangat umum (ini dapat terjadi lebih dari 1 dalam 10 dosis vaksin):
- Sakit kepala
- Mual
- Nyeri pada tempat suntikan
- Kemerahan pada tempat suntikan (≤50 mm)
- Indurasi (pengerasan kulit) pada tempat suntikan (≤50 mm)
- Merasa tidak nyaman
- Gatal pada tempat suntikan.

Umum (ini dapat terjadi hingga 1 dari 10 dosis vaksin):
- Ruam
- Kemerahan pada tempat suntikan (>50 mm)
- Indurasi (pengerasan kulit) pada tempat suntikan (>50 mm)
- Demam (≥38°C)
- Kedinginan.

Tidak umum (ini dapat terjadi hingga 1 dari 100 dosis vaksin)
- Pusing.

Data pasca pemasaran
KIPI yang telah dilaporkan selama penggunaan yang dipasarkan meliputi:

- Reaksi alergi yang mungkin termasuk pembengkakan parah pada bibir, mulut, tenggorokan (yang dapat menyebabkan kesulitan menelan), kesulitan bernapas dengan mengi atau batuk, ruam dan pembengkakan pada tangan, kaki dan pergelangan kaki, kehilangan kesadaran, tekanan darah sangat rendah
- Pingsan, kejang termasuk kejang yang berhubungan dengan demam, mati rasa dan rasa lemah pada wajah, kesulitan dengan keseimbangan
- Kelopak mata atas lemah
- Gangguan pendengaran, sakit telinga, sensasi berputar
- Sakit tenggorokan
- Kulit melepuh yang disebut kondisi bulosa
- Sakit tulang
- Peradangan dan pembengkakan pada tempat suntikan, termasuk pembengkakan luas pada anggota tubuh yang disuntik, kelelahan
- Kelainan pada tes darah untuk fungsi hati
- Jatuh, cedera kepala.

Jika KIPI menjadi serius, atau jika Anda melihat terdapat KIPI yang tidak tercantum dalam leaflet ini, segera konsultasikan pada dokter atau apoteker Anda.

5. Informasi Lain

Apa kandungan *Menveo*

Setelah rekonstitusi, setiap dosis (0.5 mL) mengandung 10 mikrogram *meningococcal oligosaccharide* kelompok A dan 5 mikrogram *meningococcal oligosaccharide* kelompok C, W-135 dan Y. Semua empat kelompok terkonjugasi ke protein *Corynebacterium diphtheriae* (CRM_{197})

Bahan lain:
Serbuk
Potassium dihydrogen phosphate dan *sucrose.*

Larutan
Sodium chloride, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate dan *water for injections*.

Bagaimana bentuk dari *Menveo* dan isi kemasan

Menveo tersedia dalam bentuk serbuk dan larutan yang akan dicampurkan sebelum diinjeksi.

Serbuk berwarna putih hingga putih pudar dalam botol vial.
Larutan tidak berwarna dan jernih dalam botol vial.

Menveo tersedia dalam ukuran kemasan satu dosis: 1 vial serbuk ditambah 1 vial larutan atau dalam ukuran kemasan 5 dosis: 5 vial serbuk ditambah 5 vial larutan.

HARUS DENGAN RESEP DOKTER

Diproduksi oleh:
GSK Vaccines S.r.l., Bellaria, Rosia, Siena, Italia
Untuk GSK Vaccines S.r.l., Via Fiorentina, Siena, Italia.

Diimpor oleh:
PT Glaxo Wellcome Indonesia
Jakarta, Indonesia.

Dus, 1 dosis (2 vial) Reg. No. XXXXXXXXXXXXXX
(tiap dosis mengandung 1 vial serbuk injeksi + 1 vial larutan injeksi @0,6 mL)

Dus, 5 dosis (10 vial) Reg. No. XXXXXXXXXXXXXX
(tiap dosis mengandung 1 vial serbuk injeksi + 1 vial larutan injeksi @0,6 mL)

Version 1 – May 2022