NAME OF THE MEDICINAL PRODUCT

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

Therapeutic indications

Menveo is indicated for active immunization of adolescents and adults (from 11-65 years of age) at risk of exposure to *Neisseria meningitidis* serogroups A, C, W135 and Y to prevent invasive disease.

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

Posology and method of administration

Adults
Menveo should be administered as a single 0.5 ml injection.

Paediatric population
Menveo is indicated from the age of 11 years and above and should be administered as a single 0.5 ml injection.

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 "Special precautions for disposal and other handling".

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.

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 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.

The tip cap of the syringe contains 10% Dry Natural Rubber. Although the risk for developing allergic latex reactions is very small, healthcare professionals are encouraged to consider the benefit risk prior to administering this vaccine to patients with known history of hypersensitivity to latex.

Interaction with other medicinal products and other forms of interaction

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.

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.

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.

Undesirable effects

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=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.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Frequencies are defined as follows:
Very common: (≥ 1/10)
Common: (≥1/100 to <1/10)
Uncommon: (≥1/1,000 to <1/100)
Rare: (≥1/10,000 to <1/1,000)
Very rare: (<1/10,000)
Not known (cannot be estimated from the available data)

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Meningococcal vaccines, ATC code: Not yet assigned

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

In the pivotal study (V59P13), participants 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 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 1.

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% (780/1039); serogroup C 79% (771/977); serogroup W-135 94% (570/609); serogroup Y 81% (510/630).

Table 1: 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	1075	29 (24, 35)	75% (73, 78)
C	1483	59 (48, 73)	84% (82, 86)
W-135	1024	87 (74, 102)	96% (95, 97)
Y	1036	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 2.

Table 2: 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 dolescents 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 3: 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. Result are presented in Table 4. 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 4: 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 5: 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)

The European Me4dicines Agency has deferred the obligation to submit the results of studies with Menveo in one or more subsets of the paediatric population in meningococcal meningitis. See “Posology and method of administration” for information on paediatric use.

Pharmacokinetic properties

Not applicable.

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 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

2 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

5 x 1 Dose powder in vial (type I glass) with a stopper (halobutyl rubber) and 5 x 1 Dose solution in vial (type I glass) with a stopper (teflon rubber).
The contents of the two components (powder vial and solution vial) are to be mixed prior to vaccination providing 1 dose of 0.5 ml.
Each pack contains five doses (10 vials) .

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. Withdraw the whole content of the vial solution and use it to reconstitute the vial powder using a suitable needle for the withdrawal (21G 1 x ½). Gently shake the reconstituted vial until the vaccine is dissolved.

Withdraw the full content s of the vial into a syringe. Please note that 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 (25G 1). 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). 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). 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

Reg. No.: DKI1027900344A1

Manufactured by Novartis Vaccines and Diagnostics S.r.l., Bellaria-Rosia, 53018 Sovicille (Siena), Italy for Novartis Vaccines and Diagnostics S.r.l., Via Fiorentina 1, 53100 Siena, Italy. Imported by PT Novartis Indonesia, Jakarta, Indonesia.

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