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# MENVEO
## *NOVARTIS VACCINES & DIAGNOSTICS*

### 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* $CRM_{197}$ protein16.7 to 33.3 micrograms

(Originally contained in the solution)

- Meningococcal group C oligosaccharide 5 micrograms Conjugated to *Corynebacterium diphtheriae* $CRM_{197}$ protein7.1 to 12.5 micrograms
- Meningococcal group W135 oligosaccharide 5 micrograms Conjugated to *Corynebacterium diphtheriae* $CRM_{197}$ protein3.3 to 8.3 micrograms
- Meningococcal group Y oligosaccharide 5 micrograms Conjugated to *Corynebacterium diphtheriae* $CRM_{197}$ protein5.6 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 (2 years of age and above), adolescents and adults to prevent invasive meningococcal disease caused by *Neisseria meningitidis* groups A, C, W135 and Y.

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

#### 4.2 Posology and method of administration
Posology

- Vaccine schedule for children 2 to 10 years of age

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

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

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

Booster

Menveo may be given as a booster dose in subjects who have previously received primary vaccination with Menveo, other conjugated meningococcal vaccine or meningococcal unconjugated polysaccharide vaccine.

The need for and timing of a booster dose in subjects previously vaccinated with Menveo is to be defined based on national recommendations.

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 deltoid muscle (upper arm) in children, adolescents and adults.

It must not be administered intravascularly, subcutaneously or intradermally.

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

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

#### 4.3 Contraindications
Hypersensitivity to the active 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 4.4).

**4.4 Special warnings and precautions for use**

Before the injection of any vaccine, the person responsible for administration must take all precautions known for the prevention of allergic or any other reactions including thorough medical history and current health status. As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in case of a rare anaphylactic event following administration of the vaccine.

Menveo should under no circumstances be administered intravascularly.

Menveo will not protect against infections caused by any other serogroups of *N. meningitidis* not present in the vaccine.

As with any vaccine, a protective immune response may not be elicited in all vaccinees (see section 5.1).

In immunocompromised individuals, vaccination may not result in an appropriate protective antibody response. Menveo has not been evaluated in immunocompromised including individuals with HIV infection, complement deficiencies and individuals with functional or anatomical asplenia may not mount an immune response to meningococcal group A, C, W-135 and Y conjugate vaccines.

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.

**4.5 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.

In the adolescents (11 to 18 years of age), Menveo can be given concomitantly with tetanus, reduced diphtheria and acellular pertussis vaccine (Tdap) and human papillomavirus quadrivalent (Types 6, 11, 16 and 18) recombinant vaccine (HPV).

In this age group. Menveo has been evaluated in two co-administration studies with either Tdap alone or Tdap and HPV.

There was no evidence of an increased rate of reactogenicity or change in the safety profile of the vaccines in either study. Antibody responses to Menveo and the diphtheria, tetanus, pertussis or HPV vaccine components were not negatively affected by co-administration.

The sequential administration of Menveo one month after Tdap resulted in lower immune response for serogroup W-135 as measured by percentage of subjects with seroresponse.Since at least 95% of subjects reached hSBA ≥1:8 for serogroup W-135 post-vaccination, the clinical relevance of this observation is unknown.

In adults, Menveo can be administered concomitantly with other vaccines: combined hepatitis A/B, yellow fever, typhoid fever (Vi polysaccharide), Japanese encephalitis and rabies.

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

Concomitant administration of Menveo and other vaccines than those listed above has not been studied. Concomitant vaccines should always be administered at separate injection sites and preferably contralateral.

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

**4.6 Fertility, Pregnancy and lactation**

***Pregnancy***

Insufficient clinical data on exposed pregnancies are available.

A reproductive and developmental toxicity study has been performed in female rabbits at a dose approximately 10 times the human dose (based on body weights). There was no evidence of maternal, foetal, or postnatal developmental effects due to Menveo. 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.

***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 breast- fed infant. Therefore, Menveo may be used during breast feeding.

***Fertlity***

There were no effects on the mating performance or fertility of female rabbits in an embryofoetal and developmental toxicity study in which rabbits were intramuscularly injected with Menveo 35, 21 and 7 days prior to mating and on gestation days 7 and 20. Male fertility has not been assessed in animals.

**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 Adverse Reactions**

**Adverse Reactions from clinical trials**

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

Frequencies are defined as follows:

| | |
|---|---|
| Very common: | (≥1/10) |
| Common: | (≥1/100 to <1/10) |
| Uncommon: | (≥1/1,000 to <1/100) |
| Rare: | (≥1/10,000 to <1/1,000) |
| Very rare: | (<1/10,000) |
| Not known | (cannot be estimated from the available data) |

Children 2 to10 years of age

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

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

Metabolism and nutrition disorder:

Common: eating disorder

Nervous system disorders:

Very common: sleepiness, headache

Gastrointestinal disorders:

Common: nausea, vomiting, diarrhea

Skin and subcutaneous tissue disorders:

Common: rash

Musculoskeletal and connective tissue disorders:

Common: Myalgia, arthralgia

General disorders and administration site conditions:

Very common: irritability, malaise, injection site pain, injection site erythema (≤50 mm), injection site induration (≤50 mm)

Common: injection site erythema (>50 mm), injection site induration (>50 mm), chills, fever ≥38ºC

Uncommon: Injection site pruritus

Individuals 11 to 65 years of age

The characterization of the safety profile of Menveo in adolescents and adults is based on data from five randomized controlled clinical trials including 6401 participants (from 11-65 years of age)

Among Menveo recipients, 58.9%, 16.4%, 21.3% and 3.4% were in the 11-18 year, 19-34 year, 35-55 year and 56-65 year age groups, respectively. The two primary safety studies were randomized, active-controlled trials that enrolled participants aged 11 to 55 years (N=2663) and 19 to 55 years (N=1606), respectively.

The incidence and severity of any, local, systemic,

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

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

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

Nervous system disorders:

Very common: headache

Uncommon: dizziness

Gastrointestinal disorders:

Very common: nausea

Skin and subcutaneous tissue disorders:

Common: rash

Musculoskeletal and connective tissue disorders

Very common: Myalgia

Common: Arthralgia

General disorders and administration site conditions:

Very common: injection site pain, injection site erythema (≤50 mm), injection site induration (≤50 mm), malaise.

Common: injection site erythema (>50 mm), injection site induration (>50 mm), fever ≥38°C, chills

Uncommon: injection site pruritus

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

**Adverse reactions from post-marketing spontaneous reports**

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

Children 2 to 10 years of age

General disorders and administration site conditions: injection site swelling, including extensive swelling of the injected limb.

Nervous system disorders: febrile convulsion.

Individuals 11 to 65 years of age

Ear and labyrinth disorders: hearing impaired, ear pain, vertigo, vestibular disorder.

Eye disorders: eyelid ptosis.

General disorders and administration site conditions: injection site pruritus, pain, erythema, inflammation and swelling, including extensive swelling of the injected limb, fatigue, malaise, pyrexia.

Immune system disorders: hypersensitivity including anaphylaxis.

Injury, poisoning and procedural complications: fall, head injury.

Investigation: alanine aminotransferase increased, body temperature increased.

Musculoskeletal and connective tissue disorders: arthralgia, bone pain.

Nervous system disorders: dizziness, syncope, tonic convulsion, headache, facial paresis, balance disorder.

Respiratory, thoracic and mediastinal disorders: oropharyngeal pain.

Skin and subcutaneous tissue disorders: bullous conditions.

### 4.9 Overdose

No case of overdose has been reported.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Meningococcal vaccines, ATC code: J07AH08.

### Clinical studies

Immunogenicity

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

Immunogenicity was evaluated in randomized, multicenter, active controlled clinical trials that enrolled persons from 2 through 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

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

recipients for serogroups W-135 and Y. GMT levels were also statistically higher among Menveo recipients for serogroup C.

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).

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

Immunogenicity in adolescents

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

In another study (V59P6) conducted in 524 ado-

**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

lescents, the immunogenicity of Menveo was compared to that of ACWY-PS.

In the 11-18 year old population of the pivotal study, V59P13, the immunogenicity of a single dose of Menveo one month post vaccination is compared with the 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, the percentage of subjects with hSBA ≥ 1:8 and the ratio of GMTs were statistically higher for serogroups A, W-135, and Y in the Menveo group, as compared to the ACWY-D group (Table 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 hSBA ≥1:8 after a dose of Menveo were as follows: serogroup A 75% (780/1039); serogroup C 80% (735/923); serogroup W-135 94% (570/609); serogroup Y 81% (510/630).

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 4).

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

**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.

| Table 4: 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 (22, 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 (75, 133) | 34 (27, 44) | - | 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.

| Table 5: Persistence of immune responses approximately 21 months, 3 years and 5 years after vaccination with Menveo (subjects were aged 11-18 years at the time of vaccination) | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Serogroup** | **Timepoint** | **Percentages of subjects with hSBA≥1:8** | | | **hSBA GMTs** | | |
| | | **Menveo** | **ACWY-D** | **P Value Menveo vs ACWY-D** | **Menveo** | **ACWY-D** | **P Value Menveo vs ACWY-D** |
| **A** | | **N=102** | **N=60** | | **N=102** | **N=60** | |
| | 21 months | 44 (34, 54) | 27 (16, 40) | 0.027 | 6.46 (4.7, 8.88) | 4.12 (2.84, 5.99) | 0.042 |
| | 3 years | 37 (28, 47) | 18 (10, 30) | 0.011 | 5.51 (3.89, 7.81) | 3.69 (2.45, 5.55) | 0.096 |
| | 5 years | 34 (25, 44) | 37 (25, 50) | 0.76 | 4.36 (3.09, 6.14) | 4.92 (3.29, 7.37) | 0.61 |
| **C** | | **N=102** | **N=59** | | **N=102** | **N=59** | |
| | 21 months | 61 (51, 70) | 63 (49, 75) | 0.81 | 11 (8.01, 14) | 7.62 (5.38, 11) | 0.095 |
| | 3 years | 68 (58, 77) | 68 (54, 79) | 0.98 | 16 (11, 26) | 17 (10, 29) | 0.86 |
| | 5 years | 64 (54, 73) | 63 (49, 75) | 0.90 | 14 (8.74, 24) | 20 (11, 35) | 0.36 |
| **W-135** | | **N=101** | **N=57** | | **N=101** | **N=57** | |
| | 21 months | 86 (78, 92) | 60 (46, 72) | <0.001 | 18 (14, 25) | 9.3 (6.59, 13) | <0.001 |
| | 3 years | 85 (77, 91) | 65 (51, 77) | 0.003 | 31 (21, 46) | 17 (11, 28) | 0.041 |
| | 5 years | 85 (77, 91) | 70 (57, 82) | 0.025 | 32 (21, 47) | 19 (12, 31) | 0.081 |
| **Y** | | **N=102** | **N=60** | | **N=102** | **N=60** | |
| | 21 months | 71 (61, 79) | 53 (40, 66) | 0.027 | 14 (10, 19) | 6.83 (4.76, 9.79) | <0.001 |
| | 3 years | 69 (59, 77) | 55 (42, 68) | 0.082 | 14 (9.68, 20) | 7.17 (4.68, 11) | 0.009 |
| | 5 years | 67 (57, 76) | 55 (42, 68) | 0.14 | 13 (8.71, 20) | 8.11 (4.98, 13) | 0.092 |

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 with 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 8).

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%

**Table 6: Persistence of immune responses approximately 12 months and 5 years after vaccination with Menveo and ACWY-PS (subjects were aged 11-18 years at the time of vaccination)**

| Serogroup | Timepoint | Percentages of subjects with hSBA≥1:8 | | | hSBA GMTs | | |
|---|---|---|---|---|---|---|---|
| | | Menveo | ACWY-PS | P Value Menveo vs ACWY-PS | Menveo | ACWY-PS | P Value Menveo vs ACWY-D |
| **A** | | **N=140** | **N=149** | | **N=50** | **N=50** | |
| | 12 months | 29% (22, 38) | 36% (29, 45) | 0.73 | 4.24 (3.35, 5.38) | 5.65 (4.54, 7.03) | 0.54 |
| | 5 years | 30% (18, 45) | 44% (30, 59) | 0.15 | 5.38 (3.29-8.78) | 7.75 (4.83-12) | 0.24 |
| **C** | | **N=140** | **N=147** | | **N=50** | **N=50** | |
| | 12 months | 77% (69, 84) | 61% (53, 69) | <0.001 | 28 (19, 41) | 26 (18, 37) | 0.22 |
| | 5 years | 76% (62, 87) | 62% (47, 75) | 0.042 | 21 (12-37) | 20 (12-35) | 0.92 |
| **W-135** | | **N=138** | **N=141** | | **N=50** | **N=50** | |
| | 12 months | 93% (88, 97) | 68% (60, 76) | <0.001 | 40 (31, 52) | 17 (13, 22) | <0.001 |
| | 5 years | 72% (58, 84) | 56% (41, 70) | 0.093 | 30 (18-52) | 13 (7.65-22) | 0.012 |
| **Y** | | **N=139** | **N=147** | | **N=50** | **N=50** | |
| | 12 months | 82% (75, 88) | 55% (47, 63) | 0.001 | 30 (22, 41) | 13 (9.49, 17) | <0.001 |
| | 5 years | 76% (62, 87) | 50% (36, 64) | 0.002 | 30 (18-49) | 8.25 (5.03-14) | <0.001 |

**Table 7: Response to Booster: bactericidal antibody responses to Menveo booster administered at 3 or 5 years after the primary vaccination with Menveo or ACWY-D or ACWY-PS in subjects aged 11-17 years**

| Sero-group | Time point | Percentages of subjects with hSBA≥1:8 | | | | hSBA GMTs | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | V59P13E1 (3 years post vaccination) | | V59P6E1 (5 years post vaccination) | | V59P13E1 (3 years post vaccination) | | V59P6E1 (5 years post vaccination) | |
| | | Menveo | ACWY-D | Menveo | ACWY-PS | Menveo | ACWY-D | Menveo | ACWY-PS |
| **A** | | **N=42** | **N=30** | **N=48-49** | **N=49** | **N=42** | **N=30** | **N=48-49** | **N=49** |
| | Pre-booster | 21% (10-37) | 20% (8-39) | 29% (17-43) | 43% (29-58) | 2.69 (1.68-4.31) | 2.81 (1.68-4.69) | 5.16 (3.46-7.7) | 7.31 (4.94-11) |
| | 7 days | - | - | 100% (93-100) | 73% (59-85) | - | - | 1059 (585-1917) | 45 (25-80) |
| | 28 days | 100% (92-100) | 100% (88-100) | 98% (89-100) | 94% (83-99) | 326 (215-494) | 390 (248-614) | 819 (514-1305) | 147 (94-232) |
| | 2 years | 79% (63-90) | 77% (58-90) | - | - | 22 (12-41) | 20 (10-39) | - | - |
| **C** | | **N=42** | **N=30** | **N=49** | **N=49** | **N=42** | **N=30** | **N=49** | **N=49** |
| | Pre-booster | 55% (39-70) | 60% (41-77) | 78% (63-88) | 61% (46-75) | 16 (8.66-31) | 15 (7.46-30) | 20 (13-33) | 19 (12-31) |
| | 7 days | - | - | 100% (93-100) | 78% (63-88) | - | - | 1603 (893-2877) | 36 (20-64) |
| | 28 days | 100% (92-100) | 100% (88-100) | 100% (93-100) | 84% (70-93) | 597 (352-1014) | 477 (268-849) | 1217 (717-2066) | 51 (30-86) |
| | 2 years | 95% (84-99) | 87% (69-96) | - | - | 124 (62-250) | 61 (29-132) | - | - |
| **W-135** | | **N=41** | **N=29** | **N=49** | **N=49** | **N=41** | **N=29** | **N=49** | **N=49** |
| | Pre-booster | 88% (74-96) | 83% (64-94) | 73% (59-85) | 55% (40-69) | 37 (21-65) | 21 (11-38) | 29 (17-49) | 12 (7.02-19) |
| | 7 days | - | - | 100% (93-100) | 84% (70-93) | - | - | 1685 (1042-2725) | 34 (21-54) |
| | 28 days | 100% (91-100) | 100% (88-100) | 100% (93-100) | 92% (80-98) | 673 (398-1137) | 1111 (631-1956) | 1644 (1090-2481) | 47 (32-71) |
| | 2 years | 100% (91-100) | 97% (82-100) | - | - | 93 (58-148) | 110 (67-183) | - | |
| **Y** | | **N=42** | **N=30** | **N=48-49** | **N=49** | **N=42** | **N=30** | **N=48-49** | **N=49** |
| | Pre-booster | 74% (58-86) | 53% (34-72) | 78% (63-88) | 51% (36-66) | 14 (8.15-26) | 8.9 (4.76-17) | 28 (18-45) | 7.8 (4.91-12) |
| | 7 days | - | - | 98% (89-100) | 76% (61-87) | - | - | 2561 (1526-4298) | 21 (13-35) |
| | 28 days | 100% (92-100) | 100% (88-100) | 100% (93-100) | 96% (86-100) | 532 (300-942) | 454 (243-846) | 2092 (1340-3268) | 63 (41-98) |
| | 2 years | 95% (84-99) | 93% (78-99) | - | - | 55 (30-101) | 46 (24-89) | - | - |

**Table 8: 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.

**Table 9: 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.

(582/875); serogroup C 71% (401/563); serogroup W135 82% (131/160); serogroup Y 66% (173/263).

Immunogenicity in older adults

See Table 9. 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 9).

**5.2 Non-clinical safety data**

Non-clinical data reveal no special hazard for humans based on animal studies that are appropriate for the safety assessment of vaccines.

## 6. PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**

Powder (vial):

Sucrose
Potassium dihydrogen phosphate

Solution (syringe or vial):

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 6.6.

**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.

Protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

**6.5 Nature and contents of container**

Powder in vial (type I glass) with a stopper (halobutyl rubber) and solution in vial (type I glass) with a stopper (butyl rubber).The contents of the two components (powder vial and solution vial) are to be mixed prior to vaccination providing one dose of 0.5 ml.

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

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

**Instructions for use and handling**

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

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

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

Using a syringe and a suitable needle (21G, 1½ inch length or a 21G, 40 mm length) withdraw the entire content 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.

**Special Precautions for disposal**

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

**7. MARKETING AUTHORISATION HOLDER**
Novartis Vaccines and Diagnostics S.r.l.
Via Fiorentina 1
53100 Siena, Italy

**8. MARKETING AUTHORISATION NUMBERS**
EU/1/10/614/001

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
15 March 2010

**10. DATE OF REVISION OF THE TEXT**
Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.ema.europa.eu