For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

MENVEO

1. NAME OF THE MEDICINAL PRODUCT

Meningococcal Group A, C, W135 and Y Conjugate Vaccine Ph. Eur.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml of the reconstituted vaccine) contains:

(Originally contained in the powder)

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

(Originally contained in the solution)

• Meningococcal group C oligosaccharide	5 micrograms
Conjugated to *Corynebacterium diphtheriae* CRM_{197} protein	7.1 to 12.5 micrograms
• Meningococcal group W-135 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solution for injection.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

MENVEO is indicated for active immunization of children (from 2 years of age), adolescents and adults to prevent invasive meningococcal disease caused by *Neisseria Meningitidis* groups A, C, W-135 and Y.

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

4.2. Posology and Method of Administration

Posology

Children (from 2 years of age), adolescents and adults

MENVEO should be administered as a single dose (0.5 ml).

To ensure optimal antibody levels against all vaccine serogroups, the primary vaccination schedule with *MENVEO* should be completed one month prior to risk of exposure to *Neisseria meningitides* groups A, C, W-135 and Y. Bactericidal antibodies (hSBA≥1:8) were observed in at least 64% of subjects at 1 week post vaccination (see *Section 5.1 Pharmacodynamic Properties* for immunogenicity data per individual serogroups).

Older people

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

Booster vaccination

Long-term antibody persistence data following vaccination with *MENVEO* are available up to 5 years after vaccination (see *Section 4.4 Special Warnings and Precautions for Use* and *Section 5.1 Pharmacodynamic Properties*).

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.

Pediatric population (under 2 years of age)

The safety and efficacy of *MENVEO* in children under 2 years of age has not yet been established.

Currently available data are described in *Section 5.1 Pharmacodynamic Properties* but no recommendation on a posology can be made.

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 medicinal product before administration, see *Section 6.6. Special Precautions for Disposal and Other Handling*.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in *Section 6.1 List of Excipients*, or diphtheria toxoid (CRM_{197}), or a life-threatening reaction after previous administration of a vaccine containing similar components (see *Section 4.4 Special Warnings and Precautions for Use*).

As with other vaccines, *MENVEO* should be postponed in individuals suffering from an acute severe febrile illness. The presence of a minor infection is not a contraindication.

4.4. Special Warnings and Precautions for Use

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

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection (see *Section 4.8 Undesirable Effects*). It is important that procedures are in place to avoid injury from fainting.

MENVEO should under no circumstances be administered intravascularly.

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

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

Studies with *MENVEO* have shown a waning of serum bactericidal antibody titers against serogroup A when using human complement in the assay (hSBA) (see *Section 5.1 Pharmacodynamic Properties*). The clinical relevance of the waning of hSBA serogroup A antibody titers is unknown. If an individual is expected to be at particular risk of exposure to Men A and received a dose of *MENVEO* more than approximately one year previously, consideration may be given to administering a booster dose.

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, W-135 and Y conjugate vaccines.

Individuals with familial complement deficiencies (for example, C3 or C5 deficiencies) and individuals receiving treatments that inhibit terminal complement activation (for example, eculizumab) are at increased risk for invasive disease caused by *Neisseria meningitidis* group A, C, W-135 and Y, even if they develop antibodies following vaccination with *MENVEO*.

MENVEO has not been evaluated in persons with thrombocytopenia, bleeding disorders or that are receiving anticoagulant therapy, because of the risk of haematoma. The risk-benefit ratio for persons at risk of haematoma following intramuscular injection must be evaluated by health care professionals.

4.5. Interaction with Other Medicinal Products and Other Forms of Interaction

MENVEO can be given concomitantly with any of the following vaccines: monovalent and combined hepatitis A and B, yellow fever, typhoid fever (Vi polysaccharide), Japanese encephalitis and rabies.

In 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 W-135 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.

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*.

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

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

4.6. 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-135 and Y, pregnancy should not preclude vaccination when the risk of exposure is clearly defined.

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

Therefore, *MENVEO* may be used during breast feeding.

4.7. Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. Dizziness has been very rarely reported following vaccination. This may temporarily affect the ability to drive or use machines.

4.8. Undesirable Effects

Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.
Frequencies are defined as follows:
Very common: (≥1/10)
Common: (≥1/100 to <1/10)
Uncommon: (≥1/1,000 to <1/100)
Rare: (≥1/10,000 to <1/1,000)
Very rare: (<1/10,000)

Not known (cannot be estimated from the available data)

Adverse reactions from clinical trials

Children 2 to 10 years of age

Overall 3464 subjects aged 2 to10 years were exposed to *MENVEO* in completed clinical trials. The characterization of the safety profile of *MENVEO* in children 2 to 10 years of age is based on data from four clinical trials in which 3181 subjects received *MENVEO*.

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

Metabolism and nutrition disorders:

Common: eating disorder

Nervous system disorders:

Very common: sleepiness, headache

Gastrointestinal disorders:

Common: nausea, vomiting, diarrhea

Skin and subcutaneous tissue disorders:

Common: rash

Musculoskeletal and connective tissue disorders:

Common: myalgia, arthralgia

General disorders and administration site conditions:

Very common: irritability, malaise, injection site pain, injection site erythema (≤50 mm), injection site induration (≤50 mm)
Common: injection site erythema (>50mm), injection site induration (>50mm), chills, fever ≥38°C
Uncommon: injection site pruritus

Individuals 11 to 65 years of age

The characterization of the safety profile of *MENVEO* in adolescents and adults is based on data from five randomised controlled clinical trials including 6401 participants (from 11-65 years of age) who received *MENVEO.* Among *MENVEO* recipients, 58.9%, 16.4%, 21.3% and 3.4% were in the 11-18 year, 19-34 year, 35-55 year and 56-65 year age groups, respectively. The two primary safety studies were randomised, 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* recipient subjects aged 11-55.

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

The list provided below presents adverse reactions reported in three pivotal and two supportive clinical trials 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.

Post-marketing experience *(all age groups)*

Blood and lymphatic system disorders

Rare: lymphadenopathy

Immune system disorders

Not known: hypersensitivity including anaphylaxis

Nervous system disorders

Not known: tonic convulsion, febrile convulsion, syncope

Ear and labyrinth disorders

Not known: vertigo

General disorders and administration site conditions

Not known: injection site cellulitis, injection site swelling, including extensive swelling of the injected limb

4.9. Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Meningococcal vaccines, ATC code: J07AH08.

Immunogenicity

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

Immunogenicity was evaluated in randomised, multicenter, active controlled clinical trials that enrolled children (2-10 years of age), adolescents (11-18 years of age), adults (19-55 years of age) and older adults (56-65 years of age).

Immunogenicity in children 2 to 10 years of age

In the pivotal study V59P20 immunogenicity of *MENVEO* was compared to ACWY-D; 1170 children were vaccinated with *MENVEO* and 1161 received the comparator vaccine in the per protocol populations. In two supportive studies V59P8 and V59P10 immunogenicity of *MENVEO* was compared to ACWY-PS.

In the pivotal, randomised, 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. Immunogenicity results one month after *MENVEO* vaccination among subjects aged 2-5 years and 6-10 years are summarized below in Table 1.

Table 1: Serum bactericidal antibody responses following *MENVEO* one month after vaccination among subjects aged 2-5 years and 6-10 years

Serogroup	2-5 years		6-10 years	
	hSBA≥1:8 (95% CI)	**hSBA GMTs (95% CI)**	**hSBA≥1:8 (95% CI)**	**hSBA GMTs (95% CI)**
A	N= 606	N= 606	N= 551	N= 551
	72% (68, 75)	26 (22, 30)	77% (74, 81)	35 (29, 42)
C	N= 607	N= 607	N= 554	N= 554
	68% (64, 72)	18 (15,20)	77% (73, 80)	36 (29, 45)

W-135	N= 594	N= 594	N= 542	N= 542
	90% (87, 92)	43 (38, 50)	91% (88, 93)	61 (52, 72)
Y	N= 593	N= 593	N= 545	N= 545
	76% (72, 79)	24 (20, 28)	79% (76, 83)	34 (28, 41)

In another randomised, 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).

The clinical relevance of higher post-vaccination immune responses is not known.

Table 2: Immunogenicity of one dose of *MENVEO* or ACWY-PS in subjects 2 through 10 years of age, measured at one month and twelve months post-vaccination

Serogroup	**1 month post-vaccination**				**12 months post-vaccination**			
	hSBA≥1:8 (95% CI)		**hSBA GMTs (95% CI)**		**hSBA≥1:8 (95% CI)**		**hSBA GMTs (95% CI)**	
	MENVEO	**ACWY-PS**	***MENVEO***	**ACWY-PS**	***MENVEO***	**ACWY-PS**	***MENVEO***	**ACWY-PS**
A	N=280	N=281	N=280	N=281	N=253	N=238	N=253	N=238
	79% (74, 84)	37% (31, 43)	36 (30, 44)	6.31 (5.21, 7.64)	23% (18, 29)	13% (9, 18)	3.88 (3.39,4.44)	3 (2.61,3.44)
C	N=281	N=283	N=281	N=283	N=252	N=240	N=252	N=240
	73% (68,78)	54% (48,60)	26 (21,34)	15 (12,20)	53% (47,59)	44% (38,51)	11 (8.64,13)	9.02 (7.23,11)
W-135	N=279	N=282	N=279	N=282	N=249	N=237	N=249	N=237
	92% (88, 95)	66% (60, 71)	60 (50, 71)	14 (12, 17)	90% (86, 94)	45% (38, 51)	42 (35, 50)	7.57 (6.33, 9.07)
Y	N=280	N=282	N=280	N=282	N=250	N=239	N=250	N=239
	88% (83, 91)	53% (47, 59)	54 (44, 66)	11 (9.29, 14)	77% (71, 82)	32% (26, 38)	27 (22, 33)	5.29 (4.34, 6.45)

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.

A randomised, observer-blind study was conducted in children 12 to 59 months of age in Finland and Poland (V59P7). A total of 199 subjects 2-5 years of age were in the *MENVEO*

per protocol immunogenicity population and 81 subjects 3-5 years of age were in the ACWY-PS group.

At 1 month post-first vaccination, the percentages of subjects with hSBA ≥ 1:8 were consistently higher in the *MENVEO* group for all four serogroups (63% vs 39%, 46% vs 39%, 78% vs 59%, and 65% vs 57% for *MENVEO* as compared to ACWY-PS for serogroups A, C, W-135, and Y, respectively).

In a randomized, observer-blind study (V59_57) conducted in US, immunogenicity of a 2-dose series and a single dose of *MENVEO* was compared in children 2 through 5 and 6 through 10 years of age (N=715).

At baseline, the percentage of subjects with hSBA ≥1:8 across the two age strata was 1%-5% for serogroup A, 13%-28% for serogroup C, 42%-64% for serogroup W-135, and 6%-19% for serogroup Y. At 1 month post last vaccination, the percentages of subjects with hSBA ≥1:8 in the 2-dose group and in the single dose group across the two age strata were: 90%-95% vs 76%–80% for serogroup A, 98%-99% vs 76%-87% for serogroup C, 99% vs 93%-96% for serogroup W-135, and 96% vs 65%-69% for serogroup Y. GMTs were higher in the 2-dose group than the single dose group at 1 month after vaccination in both age strata; however, this difference was less pronounced in the older age stratum.

At 1 year post last vaccination, the percentages of subjects with hSBA ≥1:8 after the 2-dose series and the single dose were both lower than at 1 month post-vaccination (30% after the 2-dose series, 11%-20% after the single dose for serogroup A; 61%-81% and 41%-55% for serogroup C; 92%-94% and 90%-91% for serogroup W-135; 67%-75% and 57%-65% for serogroup Y). The differences between hSBA GMTs in the 2-dose and the single dose groups at 1 year after vaccination were lower than those seen at 1 month post-vaccination.

The clinical benefit of a 2-dose vaccination series in children 2 through 10 years of age is not known.

Persistence of immune response and booster response in children 2 to 10 years of age

Antibody persistence at 5 years after primary vaccination was assessed in study V59P20E1, this was an extension of study V59P20. There was antibody persistence observed against serogroups C, W-135 and Y, with the percentages of subjects with hSBA ≥ 1:8 being 32% and 56% against serogroup C in subjects 2-5 and 6-10 years of age, respectively, 74% and 80% against serogroup W-135, and 48% and 53% against serogroup Y. GMTs were respectively 6.5 and 12 for serogroup C, 19 and 26 for serogroup W-135, and 8.13 and 10 for serogroup Y. For serogroup A, 14% and 22% of subjects 2-5 and 6-10 years of age, respectively, had hSBA ≥ 1:8 (GMTs 2.95 and 3.73).

The children also received a booster dose of *MENVEO*, 5 years after a single dose primary vaccination.
All subjects in both age groups had hSBA ≥ 1:8 across all serogroups, with antibody titers several fold higher than seen after the primary vaccination (Table 3).

Table 3: Persistence of immune responses 5 years after primary vaccination with *MENVEO*, and immune response 1 month after a booster dose among subjects aged 2-5 years and 6-10 years at the time of primary vaccination

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

Immunogenicity in individuals 11 years of age and above

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

In another study (V59P6) conducted in 524 adolescents, the immunogenicity of *MENVEO* was compared to that of ACWY-PS.

Immunogenicity in adolescents

In the 11-18-year-old population of the pivotal study, V59P13, the immunogenicity of a single dose of *MENVEO* one month post vaccination is compared with the ACWY-D. Immunogenicity results at one month after *MENVEO* are summarized below in Table 4.

Table 4: 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	1396	50 (39, 65)	85% (83, 87)
W-135	1024	87 (74, 102)	96% (95, 97)
Y	1036	51 (42, 61)	88% (85, 90)

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 randomised to receive either *MENVEO* or ACWY-PS. *MENVEO* was shown to be non-inferior to ACWY-PS vaccine for all four serogroups (A, C, W-135 and Y) based on seroresponse, proportions achieving hSBA ≥1:8, and GMTs.

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

Serogroup	**hSBA≥1:8 (95% CI)**		**hSBA GMTs (95% CI)**	
	MENVEO	**ACWY-PS**	***MENVEO***	**ACWY-PS**
A	N=140	N=149	N=140	N=149
	81% (74, 87)	41% (33, 49)	33 (25, 44)	7.31 (5.64, 9.47)
C	N=140	N=147	N=140	N=147
	84% (77, 90)	61% (53, 69)	59 (39, 89)	28 (19, 41)
W-135	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 ≥1:8 for serogroups C, W-135, and Y, with comparable levels for serogroup A. Similar findings were observed in the comparison of hSBA GMTs.

Persistence of immune response and booster response in adolescents

In study V59P13E1, the persistence of immune responses against serogroups A, C, W-135 and Y was assessed at 21 months, 3 years and 5 years post primary vaccination among subjects aged 11-18 years at the time of vaccination. The percentages of subjects with hSBA ≥ 1:8 remained constant against serogroups C, W-135, and Y from 21 months to 5 years postvaccination in the *MENVEO* group and decreased slightly over time against serogroup A (Table 6). At 5 years after primary vaccination, there were significantly higher percentages of subjects with hSBA ≥ 1:8 in the *MENVEO* group than in the vaccine-naive control subjects against all the four serogroups.

Table 6: 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	***MENVEO***
A		N=100	N=100
	21 months	45 (35, 55)	6.57 (4.77-9.05)
	3 years	38 (28, 48)	5.63 (3.97-7.99)
	5 years	35 (26, 45)	4.43 (3.13-6.26)
C		N=100	N=100
	21 months	61 (51, 71)	11 (8.12-15)
	3 years	68 (58, 77)	16 (11-25)
	5 years	64 (54, 73)	14 (8.83-24)
W-135		N=99	N=99
	21 months	86 (77, 92)	18 (14-25)
	3 years	85 (76, 91)	31 (21-46)
	5 years	85 (76, 91)	32 (21-47)
Y		N=100	N=100
	21 months	71 (61, 80)	14 (10-19)
	3 years	69 (59, 78)	14 (9.68-20)
	5 years	67 (57, 76)	13 (8.8-20)

A booster dose of *MENVEO* was administered 3 years after primary vaccination with *MENVEO* or ACWY-D. Both groups showed a robust response to the booster dose of *MENVEO* at one month after vaccination (100% of subjects had hSBA ≥ 1:8 across serogroups) and this response largely persisted through 2 years after the booster dose for serogroups C, W-135 and Y (with 87% to 100% of subjects with hSBA ≥ 1:8 across serogroups). A small decline was observed in percentages of subjects with hSBA ≥ 1:8 against serogroup A, although percentages were still high (77% to 79%). GMTs declined over time as expected but remained between 2- and 8-fold higher than prebooster values (Table 8).

In study V59P6E1, at one year post vaccination, the percentage of *MENVEO* recipients with hSBA ≥ 1:8 remained significantly higher compared with ACWY-PS recipients for

serogroups C, W-135 and Y, and similar between the two study groups for serogroup A. hSBA GMTs for serogroups W-135 and Y were higher among *MENVEO* recipients. In 5 years post vaccination, the percentage of *MENVEO* recipients with hSBA ≥ 1:8 remained significantly higher compared with ACWY-PS recipients for serogroups C and Y. Higher hSBA GMTs were observed for serogroups W-135 and Y (Table 7).

Table 7: 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-PS**
A		N=50	N=50		N=50	N=50	
	12 months	41% (27, 56)	43% (28, 59)	0.73	5.19 (3.34, 8.09)	6.19 (3.96, 9.66)	0.54
	5 years	30% (18, 45)	44% (30, 59)	0.15	5.38 (3.29, 8.78)	7.75 (4.83, 12)	0.24
C		N=50	N=50		N=50	N=50	
	12 months	82% (68, 91)	52% (37, 68)	<0.001	29 (15, 57)	17 (8.55, 33)	0.22
	5 years	76% (62, 87)	62% (47, 75)	0.042	21 (12, 37)	20 (12, 35)	0.92
W-135		N=50	N=50		N=50	N=50	
	12 months	92% (80, 98)	52% (37, 68)	<0.001	41 (26, 64)	10 (6.41, 16)	<0.001
	5 years	72% (58, 84)	56% (41, 70)	0.093	30 (18, 52)	13 (7.65, 22)	0.012
		N=50	N=50		N=50	N=50	
Y	12 months	78% (63, 88)	50% (35, 65)	0.001	34 (20, 57)	9.28 (5.5, 16)	<0.001
	5 years	76% (62, 87)	50% (36, 64)	0.002	30 (18, 49)	8.25 (5.03, 14)	<0.001

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

A significant increase in the hSBA GMTs against all four serogroups was also observed at 7 and 28 days after the booster dose (Table 8).

Table 8: Response to Booster: bactericidal antibody responses to *MENVEO* booster administered at 3 or 5 years after the primary vaccination with *MENVEO* or ACWY-PS in subjects aged 11-17 years

Serogroup	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	*MENVEO*	ACWY-PS	*MENVEO*	*MENVEO*	ACWY-PS
A		N=42	N=49	N=49	N=42	N=49	N=49
	Pre-booster	21% (10, 37)	29% (17, 43)	43% (29, 58)	2.69 (1.68, 4.31)	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)	98% (89, 100)	94% (83, 99)	326 (215, 494)	819 (514, 1305)	147 (94, 232)
	2 years	79% (63, 90)	-	-	22 (12, 41)	-	-
C		N=42	N=49	N=49	N=42	N=49	N=49
	Pre-booster	55% (39, 70)	78% (63, 88)	61% (46, 75)	16 (8.66, 31)	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% (93, 100)	84% (70, 93)	597 (352, 1014)	1217 (717, 2066)	51 (30, 86)
	2 years	95% (84-99)	-	-	124 (62-250)	-	-
W-135		N=41	N=49	N=49	N=41	N=49	N=49
	Pre-booster	88% (74, 96)	73% (59, 85)	55% (40, 69)	37 (21, 65)	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% (93, 100)	92% (80, 98)	673 (398, 1137)	1644 (1090, 2481)	47 (32, 71)
	2 years	100% (91, 100)	-	-	93 (58, 148)	-	-
Y		N=42	N=49	N=49	N=42	N=49	N=49
	Pre-booster	74% (58, 86)	78% (63, 88)	51% (36, 66)	14 (8.15, 26)	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% (93, 100)	96% (86, 100)	532 (300, 942)	2092 (1340, 3268)	63 (41, 98)
	2 years	95% (84, 99)	-	-	55 (30, 101)	-	-

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 9. In the subset of subjects aged 19-55 years who were seronegative at baseline, the proportion of subjects who achieved

a hSBA ≥ 1:8 after a dose of *MENVEO* were as follows: serogroup A 67% (582/875); serogroup C 71% (401/563); serogroup W-135 82% (131/160); serogroup Y 66% (173/263).

Table 9: 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	902	50 (43, 59)	80% (77, 83)
W-135	484	111 (93, 132)	94% (91, 96)
Y	503	44 (37, 52)	79% (76, 83)

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

Immunogenicity in older adults

The comparative immunogenicity of *MENVEO* vs. ACWY-PS was evaluated in subjects aged 56-65 years, in study V59P17. The proportion of subjects with hSBA ≥ 1:8 was non-inferior to ACWY-PS for all four serogroups and statistically superior for serogroups A and Y (Table 10).

Table 10: 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-135	N=82	N=39
	94% (86, 98)	95% (83, 99)
Y	N=84	N=41
	88% (79, 94)	68% (52, 82)

Available data in children 2 to 23 months of age

The immunogenicity of *MENVEO* in children 2 to 23 months of age was evaluated in several studies. Although a high percentage of subjects achieved hSBA titres above 1:8 following 4-dose series of *MENVEO*, with lower percentages in studies of 2-dose series and of a single dose, *MENVEO* was compared to another meningococcal vaccine in only one pivotal study, where it failed to show a response at least equivalent to a monovalent conjugated serotype C vaccine (after a single dose at the age of 12 months). Currently available data are not sufficient to establish the efficacy of *MENVEO* in children under 2 years of age. See *Section 4.2 Posology and Method of Administration* for information on paediatric use.

5.2. Pharmacokinetic Properties

Not applicable.

5.3. Preclinical Safety Data

Non-clinical data reveal no special hazard for humans based on conventional repeated-dose and reproductive and developmental toxicity studies.

In laboratory animals, no adverse reactions were seen in vaccinated maternal rabbits or in their offspring through postnatal day 29.

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Powder: Sucrose, Potassium dihydrogen phosphate

Solution: Sodium dihydrogen phosphate monohydrate, Disodium phosphate dihydrate, sodium chloride, water for injections

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in *Section 6.6 Special Precautions for Disposal and Other Handling.*

6.3. Shelf Life

36 months

The expiry date of the vaccine is indicated on the label and packaging.

After reconstitution, the medicinal product should be used immediately. However, chemical and physical stability after reconstitution was demonstrated for 8 hours below 25°C.

6.4. Special Precautions for Storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

Keep the vials in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see *Section 6.3 Shelf Life*.

Keep out of reach of children.

6.5. Nature and Contents of Container

Powder in vial (type I glass) with a stopper (butyl rubber with fluoropolymer coated surface) and solution in vial (type I glass) with a stopper (butyl rubber).

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

All presentations may not be marketed in India.

6.6. Special Precautions for Disposal and Other Handling

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

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

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

Using a syringe and suitable needle (21G, 40 mm length or 21G, 1 ½ inch 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Pharmaceuticals Limited
Registered Office
Dr. Annie Besant Road, Worli,
Mumbai 400 030, India.

8. MARKETING AUTHORISATION NUMBER(S)

Import Permission No.: IMP-221/2016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization (Form 45): 22nd December 2016

For further information please contact:
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Version MNV/PI/IN/2020/02 dated 25 September 2020

Adapted from Menveo EU-SPC dated 21 March 2019 (GDS version 008 dated 02 October 2018).