ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Menveo powder and solution for solution for injection
Meningococcal Group A, C, W-135 and Y conjugate vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

(Originally contained in the powder)

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

(Originally contained in the solution)

• Meningococcal group C oligosaccharide	5 micrograms
Conjugated to *Corynebacterium diphtheriae* CRM_{197} protein	7.1 to 12.5 micrograms
• Meningococcal group 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 solution for injection (powder and solution for injection).
The powder is a white to off-white cake.
The solution is a colourless clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Menveo is indicated for active immunization of children (from 2 years of age), adolescents and adults at risk of exposure to *Neisseria meningitidis* groups A, C, W-135 and Y, to prevent invasive disease. The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

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 meningitidis* 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 for immunogenicity data per individual serogroups).

Older adults and elderly

There are limited data in older adults (aged 56-65 years) and there are no data in elderly (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 and 5.1).

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.

Paediatric 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 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, or diphtheria toxoid (CRM_{197}), or a life-threatening reaction after previous administration of a vaccine containing similar components (see section 4.4).

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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity and anaphylaxis

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

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). It is important that procedures are in place to avoid injury from fainting.

Menveo should under no circumstances be administered intravascularly.

Limitations of effectiveness

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).

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). 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.

Immunocompromised individuals

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.

Thrombocytopenia and coagulation disorders

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.

Excipients with known effects

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

Potassium
This medicinal product contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially ‘potassium-free’.

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, rabies and meningococcal group B (Bexsero).

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.

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 with vaccines other 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 Fertility, pregnancy and lactation

Insufficient clinical data on exposed pregnancies are available.

In non-clinical studies, Menveo had no direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Considering the severity of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W-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

Menveo has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 “Undesirable effects” may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions within 7 days after vaccination with a single dose of Menveo alone in individuals aged 2 years and above were injection-site pain (42.7%), headache (26.4%), injection-site erythema ≤ 50 mm (18.1%), malaise (17.3%), injection-site induration ≤ 50 mm (15.1%), myalgia (13.5%), and irritability (11.3%) in children aged 2 to 10 years. These adverse reactions were mostly mild or moderate in intensity.

Tabulated list of adverse reactions

The safety of Menveo in individuals aged 2 years and older was evaluated in 11 randomized studies. 12 775 individuals were included in the safety analyses. Of these, 3 334 participants aged 2 to 10 years and 9 441 participants aged 11 to 65 years were exposed to Menveo in completed clinical studies.

The following adverse reactions, as listed in Table 1 below, have been identified in clinical studies conducted with Menveo when given to individuals aged 2 years and older, and during post-marketing surveillance.

Adverse reactions are listed below by MedDRA system organ class and frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

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)

Table 1: Adverse reactions

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy[1]
Immune system disorders	Uncommon	Hypersensitivity[1]
	Not known	Anaphylaxis[1]
Metabolism and nutrition disorders	Common	Eating disorder[2]
Nervous system disorders	Very common	Headache
	Common	Sleepiness[2]
	Uncommon	Syncope[1], dizziness[3]
	Very rare	Tonic convulsion[1], febrile convulsion[1]
Ear and labyrinth disorders	Uncommon	Vertigo[1]
Gastrointestinal disorders	Common	Vomiting[2], diarrhoea[2], 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	Irritability[2], malaise, injection site pain, injection site erythema (≤ 50 mm), injection site induration (≤ 50 mm)
	Common	Fever (≥38 °C), chills, injection site erythema (> 50 mm), injection site induration (> 50 mm)
	Uncommon	Injection site pruritus, injection site swelling[1]
	Very rare	Injection site cellulitis[1], extensive swelling of the injected limb[1]

[1] Adverse reaction reported during post-marketing surveillance
[2] Reported in children 2 to 10 years of age
[3] Reported in individuals 11 to 65 years of age

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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; 1 170 children were vaccinated with Menveo and 1 161 received the comparator vaccine in the per protocol populations. In two supportive studies V59P8 and V59P10 immunogenicity of Menveo was compared to ACWY-PS.

In the pivotal, 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 summarised below in Table 2.

Table 2: 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 of age), 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 3). The clinical relevance of higher post vaccination immune responses is not known.

Table 3: 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 randomised, 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 4).

Table 4: Persistence of immune responses 5 years after primary vaccination with Menveo, and immune responses 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, 1 036)
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 (1 255, 1873)	80% (68, 89)	26 (18, 38)	100% (94, 100)	1 556 (1 083, 2 237)
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 (1 360, 2 107)	53% (40, 66)	10 (6.51, 16)	100% (94, 100)	1 442 (1 050, 1 979)

Immunogenicity in individuals 11 years of age and above

In the pivotal study (V59P13), adolescents and adults received either a dose of Menveo (N = 2 649) or the 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 summarised below in Table 5.

Table 5: Serum bactericidal antibody responses following Menveo one month after vaccination among subjects aged 11-18 years

Serogroup	N	GMT (95% CI)	hSBA ≥ 1:8 (95% CI)
A	1 075	29 (24, 35)	75% (73, 78)
C	1 396	50 (39, 65)	85% (83, 87)
W-135	1 024	87 (74, 102)	96% (95, 97)
Y	1 036	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% (780/1 039); 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 6: 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 post vaccination in the Menveo group and decreased slightly over time against serogroup A (Table 7). 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 7: 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 9).

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 8).

Table 8: 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
Y		N = 50	N = 50		N = 50	N = 50	
	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 9).

Table 9: 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)	-	1 059 (585, 1 917)	45 (25, 80)
	28 days	100% (92, 100)	98% (89, 100)	94% (83, 99)	326 (215, 494)	819 (514, 1 305)	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)	-	1 603 (893, 2 877)	36 (20, 64)
	28 days	100% (92, 100)	100% (93, 100)	84% (70, 93)	597 (352, 1 014)	1 217 (717, 2 066)	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)	-	1 685 (1 042, 2 725)	34 (21, 54)
	28 days	100% (91, 100)	100% (93, 100)	92% (80, 98)	673 (398, 1 137)	1 644 (1 090, 2 481)	47 (32, 71)
	2 years	100% (91, 100)	-	-	93 (58, 148)	-	

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
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)	-	2 561 (1 526, 4 298)	21 (13, 35)
	28 days	100% (92, 100)	100% (93, 100)	96% (86, 100)	532 (300, 942)	2 092 (1 340, 3 268)	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 10. 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 10: 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 (56 - 65 years of age)

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 11).

Table 11: 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 titers 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 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.

6.3 Shelf life

4 years

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.

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), five doses (10 vials) or ten doses (20 vials).

Not all pack sizes may be marketed.

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

GSK Vaccines S.r.l.
Via Fiorentina 1
53100 Siena, Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/10/614/002
EU/1/10/614/003
EU/1/10/614/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 March 2010
Date of latest renewal: 04 December 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Menveo solution for injection
Meningococcal Group A, C, W-135 and Y conjugate vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 mL) contains:

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

Solution for injection.
The solution is a colourless clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Menveo is indicated for active immunization of children (from 2 years of age), adolescents and adults at risk of exposure to *Neisseria meningitidis* groups A, C, W-135 and Y, to prevent invasive disease. The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

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 meningitidis* 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 for immunogenicity data per individual serogroups).

Older adults and elderly

There are limited data in older adults (aged 56-65 years) and there are no data in elderly (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 and 5.1).

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.

Paediatric 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 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 of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, or diphtheria toxoid (CRM_{197}), or a life-threatening reaction after previous administration of a vaccine containing similar components (see section 4.4).

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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity and anaphylaxis

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

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). It is important that procedures are in place to avoid injury from fainting.

Menveo should under no circumstances be administered intravascularly.

Limitations of effectiveness

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).

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). 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.

Immunocompromised individuals

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.

Thrombocytopenia and coagulation disorders

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.

Excipient with known effect

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

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, rabies and meningococcal group B (Bexsero).

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.

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 with vaccines other 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 Fertility, pregnancy and lactation

Insufficient clinical data on exposed pregnancies are available.

In non-clinical studies, Menveo had no direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Considering the severity of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W-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

Menveo has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 “Undesirable effects” may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions within 7 days after vaccination with a single dose of Menveo alone in individuals aged 2 years and above were injection-site pain (42.7%), headache (26.4%), injection-site erythema ≤ 50 mm (18.1%), malaise (17.3%), injection-site induration ≤ 50 mm (15.1%), myalgia (13.5%) and irritability (11.3%) in children aged 2 to 10 years. These adverse reactions were mostly mild or moderate in intensity.

Tabulated list of adverse reactions

The safety of Menveo in individuals aged 2 years and older was evaluated in 11 randomized studies. 12 775 individuals were included in the safety analyses, of these, 3 334 participants aged 2 to 10 years and 9 441 participants aged 11 to 65 years were exposed to Menveo in completed clinical studies.

The following adverse reactions, as listed in Table 1 below, have been identified in clinical studies conducted with Menveo when given to individuals 2 years and older, and during post-marketing surveillance.

Adverse reactions are listed below by MedDRA system organ class and frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

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)

Table 1: Adverse reactions

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy[1]
Immune system disorders	Uncommon	Hypersensitivity[1]
	Not known	Anaphylaxis[1]
Metabolism and nutrition disorders	Common	Eating disorder[2]
Nervous system disorders	Very common	Headache
	Common	Sleepiness[2]
	Uncommon	Syncope[1], dizziness[3]
	Very rare	Tonic convulsion[1], febrile convulsion[1]
Ear and labyrinth disorders	Uncommon	Vertigo[1]
Gastrointestinal disorders	Common	Vomiting[2], diarrhoea[2], 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	Irritability[2], malaise, injection site pain, injection site erythema (≤ 50 mm), injection site induration (≤ 50 mm)
	Common	Fever (≥ 38 °C), chills, injection site erythema (> 50 mm), injection site induration (> 50 mm)
	Uncommon	Injection site pruritus, injection site swelling[1]
	Very rare	injection site cellulitis[1], extensive swelling of the injected limb[1]

[1] Adverse reaction reported during post-marketing surveillance
[2] Reported in children 2 to 10 years of age
[3] Reported in individuals 11 to 65 years of age

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 of Menveo liquid

Immunogenicity of Menveo liquid, as evaluated in a phase 2b observer-blind, randomised, multicentre, controlled clinical trial in subjects aged 10 to 40 years that assessed the non-inferiority for MenA of Menveo liquid (for the product aged 24 and 30 months) to Menveo lyophilised/liquid, is presented in Table 2.

Non-inferiority of Menveo liquid to Menveo lyophilised/liquid was demonstrated for MenA as per the 2 co-primary study endpoints (between groups ratio of geometric mean titers (GMTs) at 1-month post vaccination with formulation aged 24 and 30 months).

Table 2: Serum bactericidal antibody responses 1 month after vaccination in subjects aged 10-40 years receiving Menveo liquid or Menveo lyophilised/liquid formulation

Study **(Menveo liquid product age)**	**Endpoint by Serogroup**	**Menveo liquid (95% CI)**	**Menveo lyophilised/liquid (95% CI)**	**Menveo liquid / Menveo lyophilised/liquid (95% CI)**	**Menveo liquid minus Menveo lyophilised/liquid (95% CI)**
V59_78 (24 months)**	**A**	N = 363	N = 373		
	GMT	386.66 (319.47, 467.97)	318.34 (264.14, 383.67)	1.21 (0.94, 1.57)*	-
	% hSBA ≥ 1:8	93.65 (90.70, 95.89) N = 378	92.19 (89.03, 94.67) N = 384	-	1.46 (-2.24, 5.22)
	C	N = 385	N = 377		
	GMT	143.48 (110.49, 186.30)	171.74 (131.74, 223.87)	0.84 (0.58, 1.19)	-
	% hSBA ≥ 1:8	77.58 (73.10, 81.63) N = 388	78.01 (73.52, 82.06) N = 382	-	-0.43 (-6.32, 5.46)
	W-135	N = 372	N = 388		
	GMT	62.63 (50.99, 76.92)	66.37 (54.26, 81.18)	0.94 (0.72, 1.24)	-
	% hSBA ≥ 1:8	79.43 (75.07, 83.34) N = 389	80.87 (76.62, 84.64) N = 392	-	-1.43 (-7.05, 4.18)
	Y	N = 379	N = 390		
	GMT	115.66 (94.13, 142.13)	106.47 (86.93, 130.42)	1.09 (0.82, 1.44)	-
	% hSBA ≥ 1:8	87.50 (83.77, 90.64) N = 384	85.46 (81.57, 88.80) N = 392	-	2.04 (-2.81, 6.90)
V59_78 (30 months) * **	**A**	N = 356	N = 349		
	GMT	387.06 (322.72, 464.24)	348.89 (290.09, 419.61)	1.11 (0.87, 1.42)*	-
	% hSBA ≥ 1:8	93.37 (90.37, 95.66) N = 377	94.01 (91.06, 96.21) N = 367	-	-0.64 (-4.24, 2.96)

	C	N = 376	N = 377		
	GMT	256.70 (195.29, 337.41)	226.09 (171.62, 297.85)	1.14 (0.79, 1.64)	-
	% hSBA ≥ 1:8	84.17 (80.10, 87.70) N = 379	82.85 (78.67, 86.51) N = 379	-	1.32 (-3.99, 6.64)
	W-135	N = 374	N = 366		
	GMT	83.23 (68.19, 101.60)	75.42 (61.56, 92.41)	1.10 (0.84, 1.45)	-
	% hSBA ≥ 1:8	85.86 (82.00, 89.17) N = 389	81.77 (77.54, 85.50) N = 384	-	4.09 (-1.11, 9.33)
	Y	N = 386	N = 377		
	GMT	112.38 (91.56, 137.92)	117.56 (95.39, 144.89)	0.96 (0.72, 1.26)	-
	% hSBA ≥ 1:8	88.04 (84.42, 91.08) N = 393	87.56 (83.85, 90.69) N = 386	-	0.48 (-4.16, 5.13)

* Non-inferiority criterion met (the lower limit of the two-sided 95% CI > 0.5 for the between groups ratio of GMTs at Day 29 [Menveo liquid / Menveo lyophilised/liquid]).
** refers to Part 1 of study V59_78, in which the Menveo liquid aged for 24 months was used.
*** refers to Part 2 of study V59_78, in which the Menveo liquid aged for 30 months was used.

Immunogenicity of Menveo lyophilised/liquid

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; 1 170 children were vaccinated with Menveo and 1 161 received the comparator vaccine in the per protocol populations. In two supportive studies V59P8 and V59P10 immunogenicity of Menveo was compared to ACWY-PS.

In the pivotal, 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 summarised below in Table 3.

Table 3: 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 of age), 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 4). The clinical relevance of higher post vaccination immune responses is not known.

Table 4: 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 randomised, 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 5).

Table 5: Persistence of immune responses 5 years after primary vaccination with Menveo, and immune responses 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, 1 036)
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)	1 534 (1 255, 1 873)	80% (68, 89)	26 (18, 38)	100% (94, 100)	1 556 (1 083, 2 237)
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)	1 693 (1 360, 2 107)	53% (40, 66)	10 (6.51, 16)	100% (94, 100)	1 442 (1 050, 1 979)

Immunogenicity in individuals 11 years of age and above

In the pivotal study (V59P13), adolescents and adults received either a dose of Menveo (N = 2 649) or the 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 summarised below in Table 6.

Table 6: Serum bactericidal antibody responses following Menveo one month after vaccination among subjects aged 11-18 years

Serogroup	N	GMT (95% CI)	hSBA ≥ 1:8 (95% CI)
A	1 075	29 (24, 35)	75% (73, 78)
C	1 396	50 (39, 65)	85% (83, 87)
W-135	1 024	87 (74, 102)	96% (95, 97)
Y	1 036	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% (780/1 039); 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 7).

Table 7: 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 post vaccination in the Menveo group and decreased slightly over time against serogroup A (Table 8). 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 8: 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 10).

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 9).

Table 9: 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
Y		N = 50	N = 50		N = 50	N = 50	
	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 10).

Table 10: 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)	-	1 059 (585, 1 917)	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)	-	1 603 (893, 2 877)	36 (20, 64)
	28 days	100% (92, 100)	100% (93, 100)	84% (70, 93)	597 (352, 1 014)	1 217 (717, 2 066)	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)	-	1 685 (1 042, 2 725)	34 (21, 54)
	28 days	100% (91, 100)	100% (93, 100)	92% (80, 98)	673 (398, 1 137)	1 644 (1 090, 2 481)	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)	-	2 561 (1 526, 4 298)	21 (13, 35)
	28 days	100% (92, 100)	100% (93, 100)	96% (86, 100)	532 (300, 942)	2 092 (1 340, 3 268)	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 11. 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 11: 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 (aged 56-65 years)

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 12).

Table 12: 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 titers 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 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

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

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C). Do not freeze.
Keep the vial(s) in the outer carton in order to protect from light.

Stability data indicate that the unopened vaccine is stable for up to 24 hours when stored at 25 °C. At the end of this period, Menveo liquid should be used or discarded. This information is intended to guide healthcare professionals in case of temporary temperature excursion only.

6.5 Nature and contents of container

Solution in vial (type I glass) with a bromobutyl rubber stopper coated with ethylene tetrafluoroethylene (ETFE) and a pink flip-off cap.

One dose (1 vial) or 10 doses (10 vials) per package. Each vial contains one dose of 0.5 mL.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The vaccine is a ready to use solution for injection.

The vaccine should be visually inspected before administration.

The vaccine is a colourless, clear liquid solution, essentially free from visible particles. In the event of any foreign particulate matter and/or variation of physical aspect being observed, do not administer the vaccine.

Using a syringe and a suitable needle, withdraw the entire content of the vial.

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

GSK Vaccines S.r.l.
Via Fiorentina 1
53100 Siena, Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/10/614/005
EU/1/10/614/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 March 2010
Date of latest renewal: 04 December 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

GSK Vaccines S.r.l.
Bellaria-Rosia
53018 Sovicille (SI)
Italy

Name and address of the manufacturer responsible for batch release

GSK Vaccines S.r.l.
Bellaria-Rosia
53018 Sovicille (SI)
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The marketing authorisation holder shall submit PSURs for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – POWDER IN VIAL AND SOLUTION IN VIAL

1. NAME OF THE MEDICINAL PRODUCT

Menveo powder and solution for solution for injection
Meningococcal Group A, C, W-135 and Y conjugate vaccine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution 0.5 mL dose contains:
Meningococcal group A oligosaccharides 10 micrograms conjugated to *Corynebacterium diphtheriae* CRM_{197} protein 16.7-33.3 micrograms

Meningococcal group C oligosaccharides 5 micrograms conjugated to *Corynebacterium diphtheriae* CRM_{197} protein 7.1-12.5 micrograms

Meningococcal group W-135 oligosaccharides 5 micrograms conjugated to *Corynebacterium diphtheriae* CRM_{197} protein 3.3-8.3 micrograms

Meningococcal group Y oligosaccharides 5 micrograms conjugated to *Corynebacterium diphtheriae* CRM_{197} protein 5.6-10.0 micrograms.

3. LIST OF EXCIPIENTS

Excipients: Potassium dihydrogen phosphate, sucrose, sodium chloride, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

One dose (2 vials) per package.
Five doses (10 vials) per package.
Ten doses (20 vials) per package.
One dose consists of 1 vial of MenA Lyophilised Conjugate Component to be reconstituted with 1 vial of MenCWY Liquid Conjugate Component.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular injection.
Not for intravascular, subcutaneous or intradermal injection.
Shake well before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

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

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2 °C - 8 °C).
Do not freeze.
Keep the vials in the outer carton to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirement

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GSK Vaccines S.r.l., Via Fiorentina 1, 53100 Siena, Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/614/003 - 1 dose pack
EU/1/10/614/002 - 5 doses pack
EU/1/10/614/004 - 10 doses pack

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL MENA LYOPHILISED CONJUGATE COMPONENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Menveo powder for injection
MenA Conjugate
Intramuscular use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 mL)

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL MENCWY LIQUID CONJUGATE COMPONENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Menveo solution for injection
MenCWY Conjugate
Intramuscular use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.6 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – SOLUTION IN VIAL

1. NAME OF THE MEDICINAL PRODUCT

Menveo solution for injection
Meningococcal Group A, C, W-135 and Y conjugate vaccine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 mL) contains:
Meningococcal group A oligosaccharides 10 micrograms conjugated to *Corynebacterium diphtheriae* CRM_{197} protein 16.7-33.3 micrograms

Meningococcal group C oligosaccharides 5 micrograms conjugated to *Corynebacterium diphtheriae* CRM_{197} protein 7.1-12.5 micrograms

Meningococcal group W-135 oligosaccharides 5 micrograms conjugated to *Corynebacterium diphtheriae* CRM_{197} protein 3.3-8.3 micrograms

Meningococcal group Y oligosaccharides 5 micrograms conjugated to *Corynebacterium diphtheriae* CRM_{197} protein 5.6-10.0 micrograms.

3. LIST OF EXCIPIENTS

Excipients: Sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate dihydrate, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Menveo solution for injection

1 dose (1 vial) per package. One dose per vial.
10 doses (10 vials) per package. One dose per vial.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular injection.
Not for intravascular, subcutaneous or intradermal injection.
Shake well before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial(s) in the outer carton to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GSK Vaccines S.r.l., Via Fiorentina 1, 53100 Siena, Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/614/005 - 1 dose pack
EU/1/10/614/006 - 10 doses pack

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL MENACWY LIQUID CONJUGATE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Menveo solution for injection
MenACWY Conjugate
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 mL)

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Menveo powder and solution for solution for injection
Meningococcal Group A, C, W-135 and Y conjugate vaccine

Read all of this leaflet carefully before you or your child are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This vaccine has been prescribed for you or your child only.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Menveo is and what it is used for
2. What you need to know before you or your child are given Menveo
3. How to use Menveo
4. Possible side effects
5. How to store Menveo
6. Contents of the pack and other information

1. What Menveo is and what it is used for

Menveo is a vaccine that is used for active immunization of children (from 2 years of age), adolescents and adults at risk of exposure to a bacterium named *Neisseria meningitidis* serogroups A, C, W-135 and Y, to prevent invasive disease. The vaccine works by causing your body to make its own protection (antibodies) against these bacteria.

Neisseria meningitidis serogroup A, C, W-135 and Y bacteria can cause serious and sometimes life-threatening infections such as meningitis and sepsis (blood poisoning).

Menveo cannot cause bacterial meningitis. This vaccine contains a protein (called CRM_{197}) from the bacteria that cause diphtheria. Menveo does not protect against diphtheria. This means that you (or your child) should receive other vaccines to protect against diphtheria when these are due or when advised by your doctor.

2. What you need to know before you or your child are given Menveo

Do not use Menveo if you or your child has:

- ever had an allergic reaction to the active substances or any of the other ingredients of this vaccine (listed in section 6)
- ever had an allergic reaction to diphtheria toxoid (a substance used in a number of other vaccines)
- an illness with high fever. However, a mild fever or upper respiratory infection (for example cold) itself is not a reason to delay vaccination.

Warnings and precautions:

Talk to your doctor or nurse before you or your child are given Menveo if you or your child:
- have a weakened immune system. Little is known about the effectiveness of Menveo when administered to individuals with weakened immunity due to the use of immunosuppressive medications, or HIV infection, and other possible causes. It is possible that the effectiveness of Menveo could be reduced in such individuals.
- have haemophilia or any other problem that may stop your blood from clotting properly, such as persons receiving blood thinners (anticoagulants).
- receive treatment that blocks the part of the immune system known as complement activation, such as eculizumab. Even if you have been vaccinated with Menveo you remain at increased risk of disease caused by the *Neisseria meningitidis* groups A, C, W-135 and Y bacteria.

Fainting, feeling faint or other stress-related reactions can occur as a response to any needle injection. Tell your doctor or nurse if you have experienced this kind of reaction previously.

This vaccine can only protect against meningococcal group A, C, W-135, and Y bacteria. It cannot protect against other types of meningococcal bacteria other than groups A, C, W-135 and Y, or against other causes of meningitis and sepsis (blood poisoning).

As with any vaccine, Menveo may not fully protect 100% of those who get the vaccine.

If you or your child received a dose of Menveo more than one year ago and remains at particular risk of exposure to meningococcal group A bacteria, consideration may be given to administering a booster dose to maintain protection. Your doctor will advise you if and when you should receive a booster dose.

Other medicines and Menveo

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

Menveo may be given at the same time as other vaccinations but any other injected vaccines should preferably be given into a different arm from the site of the Menveo injection.

These include the following vaccines: tetanus, reduced diphtheria and acellular pertussis (Tdap), human papillomavirus (HPV), yellow fever, typhoid fever (Vi polysaccharide), Japanese encephalitis, rabies, hepatitis A and B and meningococcal group B (Bexsero).

Menveo's effect could be diminished when administered to individuals who are taking medicines that suppress the immune system.

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

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before this medicine is given. Your doctor or nurse may still recommend that you receive Menveo if you are at high risk of infection with meningococcal group A, C, W-135 and Y bacteria.

Driving and using machines

Menveo is not likely to affect your ability to drive, cycle or use machines. However, do not drive, cycle or use any machines if you are not feeling well.

Menveo contains

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.
This medicinal product contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially 'potassium-free'.

3. How to use Menveo

Menveo will be given to you or your child by a doctor or nurse.

The vaccine is usually given into the upper arm muscle (deltoid) for children (from 2 years of age), adolescents and adults. Your doctor or nurse will take care to ensure the vaccine is not given into a blood vessel and will make sure that it is injected into muscle and not into the skin.

For children (from 2 years of age), adolescents and adults: a single (0.5 mL) injection will be given.

The safety and efficacy of Menveo in children under 2 years of age has not yet been established. There are limited data in individuals aged 56-65 and there are no data in subjects aged older than 65 years.

Please tell your doctor if you have received a previous injection with Menveo or another meningococcal vaccine. Your doctor will tell you if you need an additional injection of Menveo.

For information on the reconstitution of the vaccine see the section for medical or healthcare professionals at the end of this leaflet.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most common side effects reported during clinical studies usually lasted only one to two days and were not usually severe.

The following side effects may happen after receiving Menveo:

Very common (may affect more than 1 in 10 people): headache, muscle ache, irritability (in children from 2 to 10 years of age), generally feeling unwell, injection site pain, injection site redness (≤ 50 mm), injection site firmness (≤ 50 mm)

Common (may affect up to 1 in 10 people): fever (≥ 38 °C), vomiting (in children from 2 to 10 years of age), diarrhoea (in children from 2 to 10 years of age), nausea, chills, change in eating habits (in children from 2 to 10 years of age), sleepiness (in children from 2 to 10 years of age), joint ache, rash, injection site redness (> 50 mm), injection site firmness (> 50 mm)

Uncommon (may affect up to 1 in 100 people): allergic reactions, fainting, dizziness (in adolescents from 11 years of age and adults), balance disorder, enlarged lymph nodes, injection site itching, injection site swelling

Very rare (may affect up to 1 in 10 000 people): fits (convulsions) including fits associated with fever, infection of the skin at the injection site, extensive swelling of the injected limb

Not known (cannot be estimated from the available data): severe allergic reactions that manifest with the following symptoms: swelling of the lips, mouth, throat (which may cause difficulty in

swallowing), difficulty breathing with wheezing or coughing, rash and swelling of the hands, feet and ankles, loss of consciousness, very low blood pressure.

If a severe allergic reaction occurs tell your doctor straight away or go immediately/ take your child to the nearest Accident and Emergency department because urgent medical help may be needed.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Menveo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton after EXP.
The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze. Keep the vials in the outer carton in order to protect from light.

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

Do not throw away any medicines via wastewater or household waste. Your doctor or nurse will dispose of this medicine. These measures will help protect the environment.

6. Contents of the pack and other information

What Menveo contains

One dose (0.5 mL of the reconstituted vaccine) contains:
The active substances are:

(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

The other ingredients (excipients) are:

In the powder: potassium dihydrogen phosphate and sucrose.

In the solution: sodium chloride, sodium dihydrogen phosphate monohydrate, sodium hydrogen phosphate dihydrate and water for injection (See also end of section 2).

What Menveo looks like and contents of the pack

Menveo is a powder and a solution for injection.
Each dose of Menveo is supplied as a:
- 1 Vial containing the MenA Lyophilised Conjugate Component as a white to off-white powder
- 1 Vial containing the MenCWY Liquid Conjugate Component as clear solution
- Pack size of one dose (2 vials), five doses (10 vials) or ten doses (20 vials).

Not all pack sizes may be marketed.

The contents of the two components (vial and vial) are to be mixed prior to vaccination providing 1 dose of 0.5 mL.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
GSK Vaccines S.r.l.,
Via Fiorentina 1, 53100 Siena,
Italy

Manufacturer:
GSK Vaccines S.r.l.,
Bellaria-Rosia, 53018 Sovicille (Siena),
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in (MM/YYYY)

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Reconstitution of the vaccine

Menveo must be prepared for administration by reconstituting the powder with the solution.

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.

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. Prior to injection, change the needle with one suitable for the administration. Ensure that no air bubbles are present in the syringe before injecting the vaccine.

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.

Menveo is given as an intramuscular injection, preferably into the deltoid muscle.

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

Package leaflet: Information for the user

Menveo solution for injection
Meningococcal Group A, C, W-135 and Y conjugate vaccine

Read all of this leaflet carefully before you or your child are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This vaccine has been prescribed for you or your child only.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Menveo is and what it is used for
2. What you need to know before you or your child are given Menveo
3. How to use Menveo
4. Possible side effects
5. How to store Menveo
6. Contents of the pack and other information

1. What Menveo is and what it is used for

Menveo is a vaccine that is used for active immunization of children (from 2 years of age), adolescents and adults at risk of exposure to a bacterium named *Neisseria meningitidis* serogroups A, C, W-135 and Y, to prevent invasive disease. The vaccine works by causing your body to make its own protection (antibodies) against these bacteria.

Neisseria meningitidis serogroup A, C, W-135 and Y bacteria can cause serious and sometimes life-threatening infections such as meningitis and sepsis (blood poisoning).

Menveo cannot cause bacterial meningitis. This vaccine contains a protein (called CRM_{197}) from the bacteria that cause diphtheria. Menveo does not protect against diphtheria. This means that you (or your child) should receive other vaccines to protect against diphtheria when these are due or when advised by your doctor.

2. What you need to know before you or your child are given Menveo

Do not use Menveo if you or your child has

- ever had an allergic reaction to the active substances or any of the other ingredients of this vaccine (listed in section 6)
- ever had an allergic reaction to diphtheria toxoid (a substance used in a number of other vaccines)
- an illness with high fever. However, a mild fever or upper respiratory infection (for example cold) itself is not a reason to delay vaccination.

Warnings and precautions

Talk to your doctor or nurse before you or your child are given Menveo if you or your child:
- have a weakened immune system. Little is known about the effectiveness of Menveo when administered to individuals with weakened immunity due to the use of immunosuppressive medications, or HIV infection, and other possible causes. It is possible that the effectiveness of Menveo could be reduced in such individuals.
- have haemophilia or any other problem that may stop your blood from clotting properly, such as persons receiving blood thinners (anticoagulants).
- receive treatment that blocks the part of the immune system known as complement activation, such as eculizumab. Even if you have been vaccinated with Menveo you remain at increased risk of disease caused by the *Neisseria meningitidis* groups A, C, W-135 and Y bacteria.

Fainting, feeling faint or other stress-related reactions can occur as a response to any needle injection. Tell your doctor or nurse if you have experienced this kind of reaction previously.

This vaccine can only protect against meningococcal group A, C, W-135, and Y bacteria. It cannot protect against other types of meningococcal bacteria other than groups A, C, W-135 and Y, or against other causes of meningitis and sepsis (blood poisoning).

As with any vaccine, Menveo may not fully protect 100% of those who get the vaccine.

If you or your child received a dose of Menveo more than one year ago and remains at particular risk of exposure to meningococcal group A bacteria, consideration may be given to administering a booster dose to maintain protection. Your doctor will advise you if and when you should receive a booster dose.

Other medicines and Menveo

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

Menveo may be given at the same time as other vaccinations but any other injected vaccines should preferably be given into a different arm from the site of the Menveo injection.

These include the following vaccines: tetanus, reduced diphtheria and acellular pertussis (Tdap), human papillomavirus (HPV), yellow fever, typhoid fever (Vi polysaccharide), Japanese encephalitis, rabies, hepatitis A and B and meningococcal group B (Bexsero).

Menveo's effect could be diminished when administered to individuals who are taking medicines that suppress the immune system.

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

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before this medicine is given. Your doctor or nurse may still recommend that you receive Menveo if you are at high risk of infection with meningococcal group A, C, W-135 and Y bacteria.

Driving and using machines

Menveo is not likely to affect your ability to drive, cycle or use machines. However, do not drive, cycle or use any machines if you are not feeling well.

Menveo contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to use Menveo

Menveo will be given to you or your child by a doctor or nurse.

The vaccine is usually given into the upper arm muscle (deltoid) for children (from 2 years of age), adolescents and adults. Your doctor or nurse will take care to ensure the vaccine is not given into a blood vessel and will make sure that it is injected into muscle and not into the skin.

For children (from 2 years of age), adolescents and adults: a single (0.5 mL) injection will be given.

The safety and efficacy of Menveo in children under 2 years of age have not yet been established. There are limited data in individuals aged 56-65 and there are no data in subjects aged older than 65 years.

Please tell your doctor if you have received a previous injection with Menveo or another meningococcal vaccine. Your doctor will tell you if you need an additional injection of Menveo.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most common side effects reported during clinical studies usually lasted only one to two days and were not usually severe.

The following side effects may happen after receiving Menveo:

Very common (may affect more than 1 in 10 people): headache, muscle ache, irritability (in children from 2 to 10 years of age), generally feeling unwell, injection site pain, injection site redness (≤ 50 mm), injection site firmness (≤ 50 mm)

Common (may affect up to 1 in 10 people): fever (≥ 38 °C), vomiting (in children from 2 to 10 years of age), diarrhoea (in children from 2 to 10 years of age), nausea, chills, change in eating habits (in children from 2 to 10 years of age), sleepiness (children from 2 to 10 years of age), joint ache, rash, injection site redness (> 50 mm), injection site firmness (> 50 mm)

Uncommon (may affect up to 1 in 100 people): allergic reactions, fainting, dizziness (in adolescents from 11 years of age and adults), balance disorder, enlarged lymph nodes, injection site itching, injection site swelling

Very rare (may affect up to 1 in 10 000 people): fits (convulsions) including fits associated with fever, infection of the skin at the injection site, extensive swelling of the injected limb

Not known (cannot be estimated from the available data): severe allergic reactions that manifest with the following symptoms: swelling of the lips, mouth, throat (which may cause difficulty in swallowing), difficulty breathing with wheezing or coughing, rash and swelling of the hands, feet and ankles, loss of consciousness, very low blood pressure.

If a severe allergic reaction occurs tell your doctor straight away or go immediately/ take your child to the nearest Accident and Emergency department because urgent medical help may be needed.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Menveo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton after EXP.
The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze. Keep the vial(s) in the outer carton in order to protect from light.

Stability data indicate that the unopened vaccine is stable for up to 24 hours when stored at 25 °C. At the end of this period, Menveo liquid should be used or discarded. This information is intended to guide healthcare professionals in case of temporary temperature excursion only.

Do not throw away any medicines via wastewater or household waste. Your doctor or nurse will dispose of this medicine. These measures will help protect the environment.

6. Contents of the pack and other information

What Menveo contains

One dose (0.5 mL) contains:

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

The other ingredients (excipients) are: Sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate dihydrate and water for injections.

See section 2 “Menveo contains sodium”.

What Menveo looks like and contents of the pack

Menveo is a solution for injection.
The solution is a colourless clear solution.

The solution is provided in a vial (type I glass) with a bromobutyl rubber stopper coated with ethylene tetrafluoroethylene (ETFE) and a pink flip-off cap.

One dose (1 vial) or 10 doses (10 vials) per package. Each vial contains one dose of 0.5 mL.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
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Manufacturer:
GSK Vaccines S.r.l.,
Bellaria-Rosia, 53018 Sovicille (Siena),
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

The vaccine is a ready to use solution for injection.

The vaccine should be visually inspected before administration.

The vaccine is a colourless, clear liquid solution, essentially free from visible particles. In the event of any foreign particulate matter and/or variation of physical aspect being observed, do not administer the vaccine.

Using a syringe and a suitable needle, withdraw the entire content of the vial.

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.

Stability data indicate that the unopened vaccine is stable for up to 24 hours when stored at 25 °C. At the end of this period, Menveo liquid should be used or discarded. This information is intended to guide healthcare professionals in case of temporary temperature excursion only.