

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MENVEO safely and effectively. See full prescribing information for MENVEO.

MENVEO® [Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM₁₉₇ Conjugate Vaccine]
Solution for intramuscular injection
Initial U.S. Approval: 2010

RECENT MAJOR CHANGES

INDICATIONS AND USAGE (1) January/2011

INDICATIONS AND USAGE

MENVEO is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135. MENVEO is approved for use in persons 2 through 55 years of age. MENVEO does not prevent *N. meningitidis* serogroup B infections. (1)

DOSAGE AND ADMINISTRATION

For intramuscular injection only (0.5 ml).

MENVEO is supplied in two vials that must be combined prior to administration: reconstitute the MenA lyophilized conjugate vaccine component with the MenCYW-135 liquid conjugate vaccine component immediately before administration. (2.1)

DOSAGE FORMS AND STRENGTHS

Solution for injection (0.5-mL dose) supplied as a lyophilized vaccine component that is combined through reconstitution with a liquid vaccine component, both in single dose vials. (3)

CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of MENVEO, any component of this vaccine, or any other CRM₁₉₇, diphtheria toxoid or meningococcal-containing vaccine is a contraindication to administration of MENVEO. (4)

WARNINGS AND PRECAUTIONS

- Appropriate medical treatment must be available should an acute allergic reaction, including an anaphylactic reaction, occur following administration of MENVEO. (5.1)
- Syncope, sometimes resulting in falling injury, has been reported following vaccination with MENVEO. Vaccinees should be observed for 15 minutes after vaccine administration (5.2).

ADVERSE REACTIONS

- Common solicited adverse reactions ($\geq 10\%$) among children 2 through 10 years of age who received MENVEO were: injection site pain (31%), erythema (23%), irritability (18%), induration (16%), sleepiness (14%), malaise (12%), and headache (11%). (6.1)
- Common solicited adverse reactions ($\geq 10\%$) among adolescents and adults who received MENVEO were pain at the injection site (41%), headache (30%), myalgia (18%), malaise (16%) and nausea (10%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Vaccines at 1-877-683-4732 or VAERS at 1-800-822-7967 or <http://vaers.hhs.gov>.

DRUG INTERACTIONS

Do not mix MENVEO or any of its components with any other vaccine or diluent in the same syringe or vial. (7.1)

USE IN SPECIFIC POPULATIONS

Pregnancy: Safety and effectiveness have not been established in pregnant women. Pregnancy registry available at 1-877-311-8972. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: March 2011

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

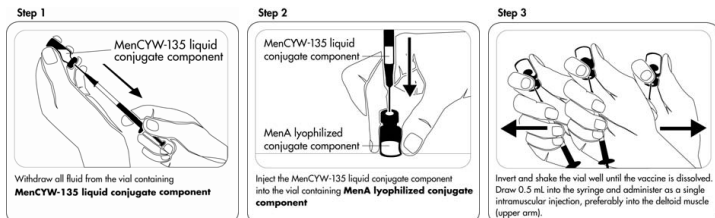
MENVEO is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135. MENVEO is approved for use in persons 2 through 55 years of age.

MENVEO does not prevent *N. meningitidis* serogroup B infections.

2 DOSAGE AND ADMINISTRATION

2.1 Reconstitution Instructions

MENVEO is supplied in two vials that must be combined prior to administration. MENVEO must be prepared for administration by reconstituting the MenA lyophilized conjugate vaccine component with the MenCYW-135 liquid conjugate vaccine component. Using a graduated syringe, withdraw the entire contents of the vial of MenCYW-135 liquid conjugate component and inject into the MenA lyophilized conjugate component vial. Invert the vial and shake well until the vaccine is dissolved 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, colorless solution, free from visible foreign particles. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If any of these conditions exist, MENVEO should not be administered.

The reconstituted vaccine should be used immediately, but may be held at or below 77°F (25°C) for up to 8 hours.

2.2 Administration

For intramuscular injection only. Do not administer MENVEO intravenously, subcutaneously or intradermally.

2.3 Dose and Schedule

MENVEO should be administered as a single 0.5 mL intramuscular injection, preferably into the deltoid muscle (upper arm). For children 2 through 5 years of age at continued high risk of meningococcal disease a second dose may be administered 2 months after the first dose (See *Clinical Trials Experience* (6.1), *Clinical Studies* (14), *Immunogenicity in Children* (14.1)). The duration of protection is not known. The persistence of bactericidal antibody has been studied through 21 months following immunization in adolescents (Table 6).

3 DOSAGE FORMS AND STRENGTHS

MENVEO is a solution for intramuscular injection (0.5 mL dose) supplied as a lyophilized vaccine component that is combined through reconstitution with a liquid vaccine component, both in single dose vials. [See *Dosage and Administration* (2), *How Supplied/Storage and Handling* (16)].

4 CONTRAINDICATIONS

Severe allergic reaction (e.g. anaphylaxis) after a previous dose of MENVEO, any component of this vaccine, or any other CRM₁₉₇, diphtheria toxoid or meningococcal-containing vaccine is a contraindication to administration of MENVEO. [See *Description* (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Appropriate medical treatment must be available should an acute allergic reaction, including an anaphylactic reaction, occur following administration of MENVEO.

5.2 Syncope

Syncope, sometimes resulting in falling injury associated with seizure-like movements has been reported following vaccination with MENVEO. Vaccinees should be observed for 15 minutes after vaccine administration to prevent and manage syncopal reactions.

5.3 Altered Immunocompetence

Safety and effectiveness of MENVEO have not been evaluated in immunocompromised persons. If MENVEO is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the expected immune response may not be obtained.

5.4 Guillain-Barré Syndrome

Following vaccination with a U.S. licensed meningococcal quadrivalent polysaccharide conjugate vaccine, an evaluation of postmarketing adverse events suggested a potential for an increased risk of Guillain-Barré Syndrome (GBS)(1). Data are not available to evaluate the potential risk of GBS following administration of MENVEO.

5.5 Bleeding Disorders

MENVEO should not be administered to persons with any bleeding disorder, or persons receiving anticoagulant therapy, unless the potential benefit outweighs the risk of administration.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The safety of MENVEO in children 2 through 10 years of age was evaluated in 4 clinical trials conducted in North America (66%), Latin America (28%) and Europe (6%) in which 3181 subjects received MENVEO and 2116 subjects received comparator vaccines (either Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined - Menomune®, Sanofi Pasteur [N=861], or Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine - Menactra®, Sanofi Pasteur [N=1255]). The subjects 2 through 10 years of age who received MENVEO were Caucasian (69%), Hispanic (13%), African American (7%), and other racial/ethnic groups (6%), 51% male, with a mean age of 5.2 years. The safety of a second dose of MENVEO administered 2 months following a first dose was studied in 351 children 2 through 5 years of age.

The safety of MENVEO in individuals 11 through 55 years of age was evaluated in 5 randomized controlled clinical trials in which 6185 participants received MENVEO alone (5286 participants), MENVEO concomitant with other vaccine(s) (899 participants), or a U.S. licensed comparator vaccine (1966 participants). In the concomitant trials MENVEO was given with Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Boostrix®, GlaxoSmithKline Biologicals) or with Boostrix plus Human Papillomavirus Quadrivalent (Types 6, 11, 16 and 18) Vaccine, Recombinant (Gardasil®, Merck & Co., Inc.). The comparator vaccine was either Menomune (209 participants) or Menactra (1757 participants). The trials were conducted in North America (46%), Latin America (41%) and Europe (13%). In two of the studies, subjects received concomitant vaccination with Boostrix, or with Boostrix plus Gardasil. Overall, subjects were Caucasian (50%), followed by Hispanic (40%), African American (7%), and other racial/ethnic groups (3%). Among MENVEO recipients, 61%, 17% and 22% were in the 11 through 18 year, 19 through 34 year and 35 through 55 year age groups, respectively, with a mean age of 23.5 years (SD 12.9 years). Among Menactra recipients, 31%, 32% and 37% were in the 11 through 18 year, 19 through 34 year and 35 through 55 year age groups, respectively, with a mean age of 29.2 years (SD 13.4 years). Among Menomune recipients, 100% were in the 11 through 18 year age group, and the mean age was 14.2 years (SD 1.8 years).

Solicited local reactions and systemic adverse events were monitored daily for 7 days following vaccination and recorded on a diary card. Participants were monitored for 28 days for unsolicited adverse events which included adverse events requiring a physician visit, Emergency Department visit or which led to a subject's withdrawal from the study. Medically significant adverse events and serious adverse events (SAE) were monitored for 6 months after vaccination.

Solicited Adverse Reactions

In clinical trials of children 2 through 10 years of age, the most frequently occurring adverse reactions ($\geq 10\%$) among all subjects who received MENVEO were injection site pain (31%), erythema (23%), irritability (18%), induration (16%), sleepiness (14%), malaise (12%), and headache (11%). Among subjects 11 through 55 years of age, the most frequently occurring adverse reactions ($\geq 10\%$) among all subjects who received MENVEO were pain at the injection site (41%), headache (30%), myalgia (18%), malaise (16%) and nausea (10%).

The rates of solicited adverse reactions reported for subjects 2 through 5 years and 6 through 10 years of age who received a single dose of MENVEO or Menactra in a randomized controlled, multicenter study conducted in the U.S. and Canada are shown in Table 1. Following a second dose of MENVEO administered to children 2 through 5 years of age, the most common solicited adverse reactions ($\geq 10\%$) were pain at injection site (28%), erythema (22%), irritability (16%), induration (13%), and sleepiness (12%). The solicited adverse events from a separate randomized controlled multicenter study conducted in the U.S. in adolescents and adults are provided in Tables 2 and 3, respectively. In neither study were concomitant vaccines administered with the study vaccines.

Table 1: Rates of solicited adverse reactions within 7-days following a single vaccination in children 2 through 5 years and 6 through 10 years of age

	Participants 2 through 5 Years of Age					
	MENVEO N = 693 %			Menactra N = 684 %		
	Any	Moderate	Severe	Any	Moderate	Severe
Local						
Injection site pain [§]	33	6	1	35	8	0.4
Erythema [¥]	27	5	1	25	3	0.3
Induration [¥]	18	2	0.4	18	2	0.3

(continued)

Table 1: Rates of solicited adverse reactions within 7-days following a single vaccination in children 2 through 5 years and 6 through 10 years of age

Participants 2 through 5 Years of Age						
	MENVEO N = 693 %			Menactra N = 684 %		
	Any	Moderate	Severe	Any	Moderate	Severe
Systemic[†]						
Irritability [§]	21	6	1	22	7	1
Sleepiness [§]	16	3	1	18	5	1
Change in eating [§]	9	2	1	10	2	0.3
Diarrhea [§]	7	1	0.1	8	1	0
Headache [§]	5	1	0	6	1	0.3
Rash [*]	4	-	-	5	-	-
Arthralgia [§]	3	1	0.1	4	1	0
Vomiting [§]	3	1	0.1	3	1	0
Fever [†]	2	0.4	0	2	0.3	0
Participants 6 through 10 Years of Age						
	MENVEO N = 582 %			Menactra N = 571 %		
	Any	Moderate	Severe	Any	Moderate	Severe
Local						
Injection site pain [§]	39	8	1	45	10	2
Erythema [‡]	28	5	1	22	2	0.2
Induration [‡]	17	2	0.3	13	2	0
Systemic[†]						
Headache [§]	18	3	1	13	2	1
Malaise [§]	14	3	1	11	3	1
Myalgia [§]	10	2	1	10	2	1
Nausea [§]	8	2	1	6	2	0.4
Arthralgia [§]	6	1	0	4	1	0.4
Chills [§]	5	1	0	5	1	0.4
Rash [*]	5	-	-	3	-	-
Fever [†]	2	1	0	2	0	0.4

[§] Moderate: Some limitation in normal daily activity, Severe: Unable to perform normal daily activity.

[‡] Moderate: ≥50-100mm, Severe: ≥ 100mm.

^{*} Rash was assessed only as present or not present, without a grading for severity.

[†] Any: ≥ 38°C, Moderate: 39-39.9°C, Severe: ≥ 40°C. Parents reported the use of antipyretic medication to treat or prevent symptoms in 11% and 13% of subjects 2 through 5 years of age, 9% and 10% of subjects 6 through 10 years of age for MENVEO and Menactra, respectively.

‡ Different systemic reactions were solicited in different age groups.

Table 2: Rates of solicited adverse reactions within 7-days following vaccination in individuals 11 through 18 years of age

Participants 11 through 18 Years of Age						
Reaction	MENVEO N = 1631 %			Menactra N = 539 %		
	Any	Moderate	Severe	Any	Moderate	Severe
Local						
Injection site pain [§]	44	9	1	53	11	1
Erythema [‡]	15	2	0.4	16	1	0
Induration [‡]	12	2	0.2	11	1	0
Systemic						
Headache [§]	29	8	2	28	7	1
Myalgia [§]	19	4	1	18	5	0.4
Nausea [§]	12	3	1	9	2	1
Malaise [§]	11	3	1	12	5	1
Chills [§]	8	2	1	7	1	0.2
Arthralgia [§]	8	2	0.4	6	1	0
Rash [*]	3	-	-	3	-	-
Fever [†]	1	0.4	0	1	0	0

[§] Moderate: Some limitation in normal daily activity, Severe: Unable to perform normal daily activity.

[‡] Moderate: ≥50-100mm, Severe: ≥ 100mm.

^{*} Rash was assessed only as present or not present, without a grading for severity.

[†] Any: ≥ 38°C, Moderate: 39-39.9°C, Severe: ≥ 40°C.

Table 3: Rates of solicited adverse reactions within 7-days following vaccination in individuals 19 through 55 years of age

Reaction	MENVEO N = 1018 %			Menactra N = 336 %		
	Any	Moderate	Severe	Any	Moderate	Severe
Local						
Injection site pain [§]	38	7	0.3	41	6	0
Erythema [‡]	16	2	1	12	1	0
Induration [‡]	13	1	0.4	9	0.3	0
Systemic						
Headache [§]	25	7	2	25	7	1
Myalgia [§]	14	4	0.5	15	3	1
Malaise [§]	10	3	1	10	2	1
Nausea [§]	7	2	0.4	5	1	0.3
Arthralgia [§]	6	2	0.4	6	1	1
Chills [§]	4	1	0.1	4	1	0
Rash [*]	2	-	-	1	-	-
Fever [†]	1	0.3	0	1	0.3	0

[§] Moderate: Some limitation in normal daily activity, Severe: Unable to perform normal daily activity.

[‡] Moderate: ≥50-100mm, Severe: ≥100mm.

^{*} Rash was assessed only as present or not present, without a grading for severity.

[†] Any: ≥ 38°C, Moderate: 39-39.9°C, Severe: ≥ 40°C.

Solicited Adverse Reactions following concomitant vaccine administration

The safety of MENVEO administered concomitantly with Boostrix and Gardasil was evaluated in a single center study conducted in Costa Rica. Solicited local and systemic adverse reactions were recorded and reported as noted above. In this study, subjects 11 through 18 years of age received MENVEO concomitantly with Boostrix and Gardasil (N=540), or MENVEO followed one month later by Boostrix and then one month later by Gardasil (N=541), or Boostrix followed one month later by MENVEO and then one month later by Gardasil (N=539). Some solicited systemic adverse reactions were more frequently reported in the group that received MENVEO, Boostrix and Gardasil concomitantly, (headache 40%, malaise 25%, myalgia 27%, and arthralgia 17%) compared to the group that first received MENVEO alone (headache 36%, malaise 20%, myalgia 19%, and arthralgia 11%). Among subjects administered MENVEO alone (one month prior to Boostrix), 36% reported headache, 20% malaise, and 16% myalgia. Among subjects administered MENVEO one month after Boostrix, 27% reported headache, 18% malaise, and 16% myalgia.

Serious Adverse Events in all safety studies

The information regarding serious adverse events in subjects 2 through 10 years of age was derived from 3 randomized, controlled clinical trials. Safety follow-up ranged from 6 through 12 months and included 2883 subjects administered MENVEO. Serious adverse events reported during the safety follow-up periods occurred in 21/2883 (0.7%) of MENVEO subjects, in 7/1255 (0.6%) of Menactra subjects, and 2/861 (0.2%) of Menomune subjects. In the subjects receiving either one or two doses of MENVEO, there were 6 subjects with pneumonia, 3 subjects with appendicitis and 2 subjects with dehydration; all other events were reported to occur in one subject. Among 1255 subjects administered a single dose of Menactra and 861 subjects administered Menomune, there were no events reported to occur in more than one subject. The serious adverse events occurring within the first 30 days after receipt of each vaccine were as follows: MENVEO (6/2883 [0.2%]) – appendicitis, pneumonia, staphylococcal infection, dehydration, febrile convulsion, and tonic convulsion; Menactra (1/1255 [0.1%]) – inguinal hernia; Menomune (2/861 [0.2%]) – abdominal pain, lobar pneumonia. In a supportive study, 298 subjects received one or two doses of MENVEO and 22 (7%) had serious adverse events over a 13 month follow-up period including 13 subjects with varicella and 2 subjects with laryngitis. All other events were reported to occur in one subject. During the 30 days post vaccination in this study, one limb injury and one case of varicella were reported.

The information regarding serious adverse events in subjects 11 through 55 years of age was derived from 5 randomized, controlled clinical trials. Serious adverse events reported within 6 months of vaccination occurred in 40/6185 (0.6%) of MENVEO subjects, 13/1757 (0.7%) of Menactra subjects, and 5/209 (2.4%) of Menomune subjects. During the 6 months following immunization, serious adverse events reported by more than one subject were as follows: MENVEO - appendicitis (3 subjects), road traffic accident (3 subjects), and suicide attempt (5 subjects); Menactra - intervertebral disc protrusion (2 subjects); Menomune - none. Serious adverse events that occurred within 30 days of vaccination were reported by 7 of 6185 (0.1%) subjects in the MENVEO group, 4 of 1757 (0.2%) subjects in the Menactra group, and by none of 209 subjects in the Menomune group. The events

that occurred during the first 30 days post immunization with MENVEO were: vitello-intestinal duct remnant; Cushing's syndrome; viral hepatitis; pelvic inflammatory disease; intentional multiple drug overdose; simple partial seizure; and suicidal depression. The events that occurred during the first 30 days post immunization with Menactra were: herpes zoster; fall; intervertebral disc protrusion; and angioedema.

6.2 Postmarketing Experience

In addition to reports in clinical trials, worldwide voluntary reports of adverse events received for MENVEO in persons 11 through 55 years of age since market introduction of this vaccine are listed below. This list includes serious events or events which have plausible causal connection to MENVEO. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Ear and Labyrinth Disorders: Hearing impaired, ear pain, vertigo, vestibular disorder.

Eye Disorders: Eyelid ptosis.

General Disorders and Administration Site Conditions: Injection site pruritus, pain, erythema, inflammation and swelling, fatigue, malaise, pyrexia.

Immune System Disorders: Hypersensitivity.

Infections and Infestations: Vaccination site cellulitis.

Injury, Poisoning and Procedural Complications: Fall, head injury.

Investigation: Alanine aminotransferase increased, body temperature increased.

Musculoskeletal and Connective Tissue Disorders: Arthralgia, bone pain.

Nervous System Disorders: Dizziness, syncope, tonic convulsion, headache, facial paresis, balance disorder.

Respiratory, Thoracic and Mediastinal Disorders: Oropharyngeal pain.

Skin and Subcutaneous Tissue Disorders: Skin exfoliation.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

Do not mix MENVEO or any of its components with any other vaccine or diluent in the same syringe or vial.

For children 2 through 10 years of age, no data are available to evaluate safety and immunogenicity of other childhood vaccines when administered concomitantly with MENVEO.

In a clinical trial in adolescents, MENVEO was given concomitantly with Boostrix and Gardasil, no interference was observed in meningococcal immune responses when compared to MENVEO given alone. Lower geometric mean antibody concentrations (GMCs) for antibodies to the pertussis antigens filamentous hemagglutinin (FHA) and pertactin were observed when MENVEO was administered concomitantly with Boostrix and Gardasil as compared with Boostrix alone. [*Immunogenicity of Concomitantly Administered Vaccines*, 14.4]

7.2 Immunosuppressive Treatments

Immunosuppressive therapies, such as irradiation, antimetabolite medications, alkylating agents, cytotoxic drugs, and corticosteroids (when used in greater than physiologic doses) may reduce the immune response to MENVEO [See *Altered Immunocompetence* (5.3)]. The immunogenicity of MENVEO has not been evaluated in persons receiving such therapies.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproduction studies have been performed in female rabbits at a dose of approximately 20 times the human dose (on a mg/kg basis) and have revealed no evidence of impaired fertility or harm to the fetus due to MENVEO. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, MENVEO should be given to a pregnant woman only if clearly needed.

Nonclinical Studies

The effect of MENVEO on embryo-fetal and post-natal development was evaluated in pregnant rabbits. Animals were administered MENVEO 3 times prior to gestation, during the period of organogenesis (gestation day 7) and later in pregnancy (gestation day 20), 0.5 ml/rabbit/occasion (approximately 20-fold excess relative to the projected human dose on a body weight basis) by intramuscular injections. There were no adverse effects attributable to the vaccine on mating, female fertility, pregnancy, or embryo-fetal development. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in this study.

Clinical Studies

To date, no clinical trials have been specifically designed to evaluate the use of MENVEO in pregnant or lactating women. Among the 5065 women in the adolescent and adult populations enrolled in the studies, 43 women were found to be pregnant during the 6-month follow-up period after vaccination. Of these, 37 pregnancies occurred among 3952 MENVEO recipients (7 spontaneous abortions, no congenital anomalies). Six pregnancies occurred among 1113 Menactra recipients (no spontaneous abortions, one congenital anomaly (hydrocephalus)).

Among the seven subjects with adverse pregnancy outcomes who had received MENVEO, the estimated dates of conception were 5 days prior to vaccination (1 subject), 6 to 17 weeks post vaccination (5 subjects), and 6 months post vaccination (1 subject). In the subject who had received Menactra the estimated date of conception was approximately 15 weeks post immunization.

Safety and effectiveness of MENVEO have not been established in pregnant women.

Pregnancy Registry for MENVEO

Novartis Vaccines and Diagnostics Inc. maintains a pregnancy registry to monitor the fetal outcomes of pregnant women exposed to MENVEO. To enroll in the Novartis Vaccines and Diagnostics Inc. pregnancy registry, please call 1-877-311-8972.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when MENVEO is administered to a nursing woman. No studies have been conducted to assess the impact of MENVEO on milk production, its presence in breast milk or its effects on the breast-fed child.

8.4 Pediatric Populations

Safety and effectiveness of MENVEO in children under 2 years old have not been established.

8.5 Geriatric Populations

Safety and effectiveness of MENVEO in adults 65 years of age and older have not been established.

11 DESCRIPTION

MENVEO [Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM₁₉₇ Conjugate Vaccine] is a sterile liquid vaccine administered by intramuscular injection that contains *N. meningitidis* serogroups A, C, Y and W-135 oligosaccharides conjugated individually to *Corynebacterium diphtheriae* CRM₁₉₇ protein. The polysaccharides are produced by bacterial fermentation of *N. meningitidis* (serogroups A, C, Y or W-135). *N. meningitidis* strains A, C, Y and W-135 are each cultured and grown on Franz Complete medium and treated with formaldehyde. MenA, MenW-135 and MenY polysaccharides are purified by several extraction and precipitation steps. MenC polysaccharide is purified by a combination of chromatography and precipitation steps.

The protein carrier (CRM₁₉₇) is produced by bacterial fermentation and is purified by a series of chromatography and ultrafiltration steps. *C. diphtheriae* is cultured and grown on CY medium containing yeast extracts and amino acids. The oligosaccharides are prepared for conjugation from purified polysaccharides by hydrolysis, sizing, and reductive amination. After activation, each oligosaccharide is covalently linked to the CRM₁₉₇ protein. The resulting glycoconjugates are purified to yield the four drug substances, which compose the final vaccine. The vaccine contains no preservative or adjuvant. Each dose of vaccine contains 10 µg MenA oligosaccharide, 5 µg of each of MenC, MenY and MenW-135 oligosaccharides and 32.7 to 64.1 µg CRM₁₉₇ protein. Residual formaldehyde per dose is estimated to be not more than 0.30 µg.

The vials in which the vaccine components are contained are composed of Type I glass, USP. The container closures (synthetic rubber stoppers) do not contain latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Neisseria meningitidis is a gram-negative diplococcus that causes life-threatening invasive disease such as meningitis and sepsis. Globally, 5 serogroups, A, B, C, Y and W-135 cause almost all invasive meningococcal infections. The presence of serum bactericidal antibodies protects against invasive meningococcal disease (2). Vaccination with MENVEO leads to the production of bactericidal antibodies directed against the capsular polysaccharides of serogroups A, C, Y and W-135.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

MENVEO has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility.

14 CLINICAL STUDIES

The effectiveness of MENVEO in subjects 2 through 55 years of age was assessed by comparing the serum bactericidal antibody (SBA) responses to immunization with MENVEO to those following immunization with the licensed meningococcal quadrivalent conjugate vaccine Menactra. Serogroup-specific anticapsular antibodies with bactericidal activity were measured using pooled human serum that lacked bactericidal activity as the source of exogenous complement (hSBA).

Effectiveness in subjects 2 through 10 years and 11 through 55 years of age was evaluated in two randomized, multicenter, active controlled clinical studies comparing the hSBA responses following one dose of MENVEO or Menactra. The primary effectiveness endpoint was hSBA seroresponse to each serogroup 28 days after vaccination. Seroresponse was defined as: a) post vaccination hSBA titer of $\geq 1:8$ for subjects with a baseline hSBA titer of $<1:4$; or, b) at least 4-fold higher than baseline titers for subjects with a pre-vaccination hSBA titer $\geq 1:4$. Secondary endpoints included the proportion of subjects with post vaccination hSBA titer $\geq 1:8$ and the hSBA Geometric Mean Titer (GMT) for each serogroup. In a separate group of children 2 through 5 years of age randomized to receive two doses of MENVEO administered two months apart, seroresponse rate, proportion with post-vaccination hSBA titer $\geq 1:8$ and GMT were determined for each serogroup.

The study in subjects 2 through 10 years of age was conducted in the U.S. and Canada and was stratified by age (2 through 5 years and 6 through 10 years). The per protocol population evaluated after a single dose of vaccine consisted of 1170 subjects who received MENVEO and 1161 who received Menactra (see Table 4) and included serological results for 89% to 95% of subjects, depending on serogroup and age group. Demographics were similar for the 616 and 619 subjects 2 through 5 years of age for MENVEO and Menactra: mean age 3.6 years (SD 1.1) vs. 3.6 years (SD 1.1); 51% vs. 52% male; 62% vs. 62% Caucasian, 14% vs. 13% Hispanic, 12%

vs. 13% African American, 6% vs. 4% Asian, and 7% vs. 8% other. Demographics were also similar for 554 and 542 per protocol subjects 6 through 10 years of age for MENVEO and Menactra: mean age 7.9 years (SD 1.4) vs. 8.1 years (SD 1.4); 52% vs. 56% male; 66% vs. 66% Caucasian, 14% vs. 14% African American, 7% vs. 7% Hispanic, 5% vs. 6% Asian, and 8% vs. 8% other. The per protocol population evaluated after two doses of MENVEO consisted of 297 subjects and included serologic results for 96-99% of subjects, depending on serogroup.

The study in subjects 11 through 55 years of age was a randomized, multicenter, active controlled clinical trial conducted in the U.S. and stratified by age (11 through 18 years of age and 19 through 55 years of age). This study enrolled 3539 participants, who were randomized to receive a dose of MENVEO (N=2663) or Menactra (N=876). Among subjects who completed the per-protocol evaluation for immunogenicity (N=3393, MENVEO=2549, Menactra=844), demographics for MENVEO and Menactra subjects respectively were similar: mean age 23.9 (SD 13.6) vs. 23.7 (SD 13.7), 42% vs. 42% male, 79% vs. 78% Caucasian, 8% vs. 9% African American, 7% vs. 7% Hispanic, 3% vs. 3% Asian, 2% vs. 3% other. Immunogenicity for each serogroup was assessed in a subset of study participants (see Tables 5 and 7).

14.1 Immunogenicity in Children

In study participants 2 through 5 years and 6 through 10 years of age, non-inferiority of MENVEO to Menactra for the proportion of subjects with a seroresponse was demonstrated for serogroups C, W-135 and Y, but not for serogroup A (Table 4).

Table 4: Comparison of bactericidal antibody responses[†] to MENVEO and Menactra 28 days after vaccination of subjects 2 through 5 years and 6 through 10 years of age

Endpoint by serogroup	2-5 Years			6-10 Years		
	MENVEO (95% CI)	Menactra (95% CI)	Percent Difference (MENVEO – Menactra) or GMT ratio (MENVEO/Menactra) (95% CI)	MENVEO (95% CI)	Menactra (95% CI)	Percent Difference (MENVEO – Menactra) or GMT ratio (MENVEO/Menactra) (95% CI)
A	N=606	N=611		N=551	N=541	
% Seroresponse [‡]	72 (68, 75)	77 (73, 80)	-5 (-10, -0) [§]	77 (73, 80)	83 (79, 86)	-6 (-11, -1) [§]
% ≥ 1:8	72 (68, 75)	78 (74, 81)	-6 (-11, -1)	77 (74, 81)	83 (80, 86)	-6 (-11, -1)
GMT	26 (22, 30)	25 (21, 29)	1.04 (0.86, 1.27)	35 (29, 42)	35 (29, 41)	1.01 (0.83, 1.24)
C	N=607	N=615		N=554	N=539	
% Seroresponse [‡]	60 (56, 64)	56 (52, 60)	4 (-2, 9) [*]	63 (59, 67)	57 (53, 62)	6 (0, 11) [*]
% ≥ 1:8	68 (64, 72)	64 (60, 68)	4 (-1, 10)	77 (73, 80)	74 (70, 77)	3 (-2, 8)
GMT	18 (15, 20)	13 (11, 15)	1.33 (1.11, 1.6)	36 (29, 45)	27 (21, 33)	1.36 (1.06, 1.73)
W-135	N=594	N=605		N=542	N=533	
% Seroresponse [‡]	72 (68, 75)	58 (54, 62)	14 (9, 19) [*]	57 (53, 61)	44 (40, 49)	13 (7, 18) [*]
% ≥ 1:8	90 (87, 92)	75 (71, 78)	15 (11, 19)	91 (88, 93)	84 (81, 87)	7 (3, 11)
GMT	43 (38, 50)	21 (19, 25)	2.02 (1.71, 2.39)	61 (52, 72)	35 (30, 42)	1.72 (1.44, 2.06)
Y	N=593	N=600		N=545	N=539	
% Seroresponse [‡]	66 (62, 70)	45 (41, 49)	21 (16, 27) [*]	58 (54, 62)	39 (35, 44)	19 (13, 24) [*]
% ≥ 1:8	76 (72, 79)	57 (53, 61)	19 (14, 24)	79 (76, 83)	63 (59, 67)	16 (11, 21)
GMT	24 (20, 28)	10 (8.68, 12)	2.36 (1.95, 2.85)	34 (28, 41)	14 (12, 17)	2.41 (1.95, 2.97)

[†] Serum Bactericidal Assay with exogenous human complement source (hSBA).

[‡] Seroresponse was defined as: subjects with a pre-vaccination hSBA titer of <1:4, a post vaccination titer of ≥1:8 and among subjects with a pre-vaccination hSBA titer of ≥1:4, a post vaccination titer at least 4-fold higher than baseline.

[§] Non-inferiority criterion not met (the lower limit of the two-sided 95% CI ≤ -10% for vaccine group differences).

^{*} Non-inferiority criterion met (the lower limit of the two-sided 95% CI > -10% for vaccine group differences [MENVEO minus Menactra]).

In the 297 per protocol subjects 2 through 5 years of age observed at 1 month after the second dose of MENVEO, the proportions of subjects with seroresponse (95% CI) were: 91% (87-94), 98% (95-99), 89% (85-92), and 95% (91-97) for serogroups A, C, W-135 and Y, respectively. The proportion of subjects with hSBA titers ≥ 1:8

(95% CI) were 91% (88-94), 99% (97-100), 99% (98-100), and 98% (95-99) for serogroups A, C, W-135 and Y, respectively. The hSBA GMTs (95% CI) for this group were 64 (51-81), 144 (118-177), 132 (111-157), and 102 (82-126) for serogroups A, C, W-135 and Y, respectively.

14.2 Immunogenicity in Adolescents

In study participants 11 through 18 years of age, non-inferiority of MENVEO to Menactra was demonstrated for all four serogroups for the proportion of subjects with a seroresponse (Table 5).

Table 5: Comparison of bactericidal antibody responses[†] to MENVEO and Menactra 28 days after vaccination of subjects 11 through 18 years of age

Endpoint by Serogroup	Bactericidal Antibody Response [†]		Comparison of MENVEO and Menactra	
	MENVEO (95% CI)	Menactra (95% CI)	MENVEO/Menactra (95% CI)	MENVEO minus Menactra (95% CI)
A	N=1075	N=359		
% Seroresponse [‡]	75 (72, 77)	66 (61, 71)		8 (3, 14) [*]
% ≥ 1:8	75 (73, 78)	67 (62, 72)	-	8 (3, 14)
GMT	29 (24, 35)	18 (14, 23)	1.63 (1.31, 2.02)	-
C	N=1396	N=460		
% Seroresponse [‡]	76 (73, 78)	73 (69, 77)		2 (-2, 7) [*]
% ≥ 1:8	85 (83, 87)	85 (81, 88)	-	0 (-4, 4)
GMT	50 (39, 65)	41 (30, 55)	1.22 (0.97, 1.55)	-
W-135	N=1024	N=288		
% Seroresponse [‡]	75 (72, 77)	63 (57, 68)		12 (6, 18) [*]
% ≥ 1:8	96 (95, 97)	88 (84, 92)	-	8 (4, 12)
GMT	87 (74, 102)	44 (35, 54)	2.00 (1.66, 2.42)	-
Y	N=1036	N=294		
% Seroresponse [‡]	68 (65, 71)	41 (35, 47)		27 (20, 33) [*]
% ≥ 1:8	88 (85, 90)	69 (63, 74)	-	19 (14, 25)
GMT	51 (42, 61)	18 (14, 23)	2.82 (2.26, 3.52)	-

[†] Serum Bactericidal Assay with exogenous human complement source (hSBA).

[‡] Seroresponse was defined as: a) post vaccination hSBA ≥1:8 for subjects with a pre-vaccination hSBA <1:4; or, b) at least 4-fold higher than baseline titers for subjects with a pre-vaccination hSBA ≥1:4.

^{*} Non-inferiority criterion for the primary endpoint met (the lower limit of the two-sided 95% CI > -10% for vaccine group differences [MENVEO minus Menactra]).

A subset of adolescents, who had received either MENVEO (n=275) or Menactra (n=179), was enrolled in a follow-up observational study along with separately enrolled age-matched naive subjects (n=97) to assess the persistence of antibody responses through 21 months following vaccination. Data are presented in Table 6.

Table 6: Persistence of immune responses through 21 months post vaccination among adolescents vaccinated with one dose of MENVEO or Menactra

Serogroup	% hSBA ≥1:8 (95% CI)			hSBA GMTs (95% CI)		
	MENVEO	Menactra	Naive	MENVEO	Menactra	Naive
A	N=275	N=179	N=97	N=275	N=179	N=97
	36 (30, 42)	23 (17, 30)	5 (2, 12)	5.29 (4.63, 6.05)	3.5 (2.97, 4.14)	2.36 (1.88, 2.96)
C	N=275	N=179	N=97	N=275	N=179	N=97
	62 (56, 68)	59 (52, 66)	42 (32, 53)	10 (9.02, 12)	8.96 (7.51, 11)	5.95 (4.68, 7.56)
W-135	N=273	N=176	N=97	N=273	N=176	N=97
	84 (79, 88)	74 (67, 80)	51 (40, 61)	18 (15, 20)	14 (12, 17)	7.80 (6.11, 9.97)
Y	N=275	N=179	N=97	N=275	N=179	N=97
	67 (61, 72)	54 (47, 62)	40 (30, 51)	12 (10, 14)	7.85 (6.54, 9.43)	5.14 (4.01, 6.60)

14.3 Immunogenicity in Adults

In study participants 19 through 55 years of age, non-inferiority of MENVEO to Menactra was demonstrated for all four serogroups for the proportion of subjects with a seroresponse (Table 7).

Table 7: Comparison of bactericidal antibody responses† to MENVEO and Menactra 28 days after vaccination of subjects 19 through 55 years of age

Endpoint by Serogroup	Bactericidal Antibody Response†		Comparison of MENVEO and Menactra	
	MENVEO (95% CI)	Menactra (95% CI)	MENVEO/ Menactra (95% CI)	MENVEO minus Menactra (95% CI)
A	N=963	N=321		
% Seroresponse‡	67 (64, 70)	68 (63, 73)		-1 (-7, 5)*
% ≥ 1:8	69 (66, 72)	71 (65, 76)	-	-2 (-7, 4)
GMT	31 (27, 36)	30 (24, 37)	1.06 (0.82, 1.37)	-
C	N=902	N=300		
% Seroresponse‡	68 (64, 71)	60 (54, 65)		8 (2, 14)*
% ≥ 1:8	80 (77, 83)	74 (69, 79)	-	6 (1, 12)
GMT	50 (43, 59)	34 (26, 43)	1.50 (1.14, 1.97)	-
W-135	N=484	N=292		
% Seroresponse‡	50 (46, 55)	41 (35, 47)		9 (2, 17)*
% ≥ 1:8	94 (91, 96)	90 (86, 93)	-	4 (0, 9)
GMT	111 (93, 132)	69 (55, 85)	1.61 (1.24, 2.1)	-
Y	N=503	N=306		
% Seroresponse‡	56 (51, 60)	40 (34, 46)		16 (9, 23)*
% ≥ 1:8	79 (76, 83)	70 (65, 75)	-	9 (3, 15)
GMT	44 (37, 52)	21 (17, 26)	2.10 (1.60, 2.75)	-

† Serum Bactericidal Assay with exogenous human complement source (hSBA).

‡ Seroresponse was defined as: a) post vaccination hSBA ≥1:8 for subjects with a pre-vaccination hSBA <1:4; or, b) at least 4-fold higher than baseline titers for subjects with a pre-vaccination hSBA ≥1:4.

*Non-inferiority criterion for the primary endpoint met (the lower limit of the two-sided 95% CI >-10% for vaccine group differences [MENVEO minus Menactra]).

14.4 Immunogenicity of Concomitantly Administered Vaccines

For children 2 through 10 years of age, no data are available for evaluating safety and immunogenicity of other childhood vaccines when administered concomitantly with MENVEO. For individuals 11 through 18 years of age, the effect of concomitant administration of MENVEO with Boostrix and Gardasil was evaluated in a study conducted in Costa Rica (see also section 6.1 for the safety results from this trial). Subjects were randomized to receive one of the following regimens at the start of the trial: MENVEO plus Boostrix plus Gardasil (N=540); MENVEO alone (N=541); Boostrix alone (N=539). Subjects were healthy adolescents 11 through 18 years of age (mean age between groups was 13.8 to 13.9 years). For MENVEO antigens, the proportion (95% CI) of subjects achieving an hSBA seroresponse among those who received MENVEO plus Boostrix plus Gardasil vs. MENVEO alone, respectively, were: serogroup A 80% (76, 84) vs. 82% (78, 85); serogroup C 83% (80, 87) vs. 84% (80, 87); serogroup W-135 77% (73, 80) vs. 81% (77, 84); serogroup Y 83% (79, 86) vs. 82% (79, 86). Among subjects who received Boostrix plus MENVEO plus Gardasil, compared with Boostrix alone, the proportions (95% CI) of subjects who achieved an anti-tetanus or anti-diphtheria toxoids levels ≥1.0 IU/mL in the two groups respectively were 100% (99, 100) vs. 98% (96, 99) and 100% (99, 100) vs. 100% (99, 100). For pertussis antigens, among subjects who received Boostrix plus MENVEO plus Gardasil, compared with Boostrix alone, the responses respectively for anti-pertussis toxin GMCs (95% CI) were 51 (47, 55) vs. 63 (58, 69) ELISA Units (EU)/mL, for anti-filamentous hemagglutinin were 342 (310, 376) vs. 511 (464, 563) EU/mL, and for anti-pertactin were 819 (727, 923) vs. 1197 (1061, 1350) EU/mL. Because there are no established serological correlates of protection for pertussis, the clinical implications of the lower pertussis antigen responses are unknown.

15 REFERENCES

- Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report (MMWR) (2006) 55 (41):1120-1124.
- Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. J Exp Med (1969);129:1307-1326.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

MENVEO is supplied as a vial containing MenA lyophilized conjugate component and a vial containing MenCYW-135 liquid conjugate component (1 dose after reconstitution). There are five doses (10 vials) per package. The container closures (synthetic rubber stoppers) do not contain latex.

NDC: 46028-208-01

16.2 Storage and Handling

Do not freeze. Frozen/previously frozen product should not be used.

Store refrigerated, away from the freezer compartment, at 36°F to 46°F (2°C to 8°C). Protect from light. Vaccine must be maintained at 36°F to 46°F during transport.

Do not use after the expiration date. The reconstituted vaccine should be used immediately, but may be held at or below 77°F (25°C) for up to 8 hours.

17 PATIENT COUNSELING INFORMATION

Vaccine Information Statements are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization to the patient, parent, or guardian. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

Inform patients, parents or guardians about:

- Potential benefits and risks of immunization with MENVEO.
- Potential for adverse reactions that have been temporally associated with administration of MENVEO or other vaccines containing similar components.
- Reporting any adverse reactions to their healthcare provider.
- The Novartis Vaccines and Diagnostics, Inc. pregnancy registry, as appropriate.

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