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 CRM_{197} Conjugate Vaccine]
Solution for intramuscular injection
Initial U.S. Approval: 2010

---------- 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 months 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)
- In children initiating vaccination at 2 months of age, MENVEO is to be administered as a four-dose series at 2, 4, 6, and 12 months of age. (2.3)
- In children initiating vaccination at 7 months through 23 months of age, MENVEO is to be administered as a two-dose series with the second dose administered in the second year of life and at least three months after the first dose. (2.3)
- In individuals 2 years through 55 years of age MENVEO is to be administered as a single dose. (2.3)

---------- DOSAGE FORMS AND STRENGTHS----------
Solution for intramuscular injection supplied as a lyophilized MenA conjugate vaccine component to be reconstituted with the accompanying MenCYW-135 liquid conjugate vaccine component. A single dose, after reconstitution is 0.5 mL. (3)

---------- CONTRAINDICATIONS ----------
Severe allergic reaction (e.g., anaphylaxis) after a previous dose of MENVEO, any component of this vaccine, or any other CRM_{197}-, 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 at least 15 minutes after vaccine administration. (5.2)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including MENVEO, to an infant born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination. (5.5)

---------- ADVERSE REACTIONS ----------
- Common solicited adverse reactions (≥10%) among children initiating vaccination at 2 months of age and receiving the four-dose series were tenderness (24% to 41%) and erythema at injection site (11% to 15%), irritability (42% to 57%), sleepiness (29% to 50%), persistent crying (21% to 41%), change in eating habits (17% to 23%), vomiting (5% to 11%), and diarrhea (8% to 16%). (6.1)
- Common solicited adverse reactions (≥10%) among children initiating vaccination at 7 months through 23 months of age and receiving the two-dose series were tenderness (10% to 16%) and erythema at injection site (12% to 15%), irritability (27% to 40%), sleepiness (17% to 29%), persistent crying (12-21%), change in eating habits (12% to 20%), and diarrhea (10% to 16%). (6.1)
- Common solicited adverse reactions (≥10%) among children 2 years 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 (≥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 GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.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 1-877-413-4759. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2017

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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 months through 55 years of age.

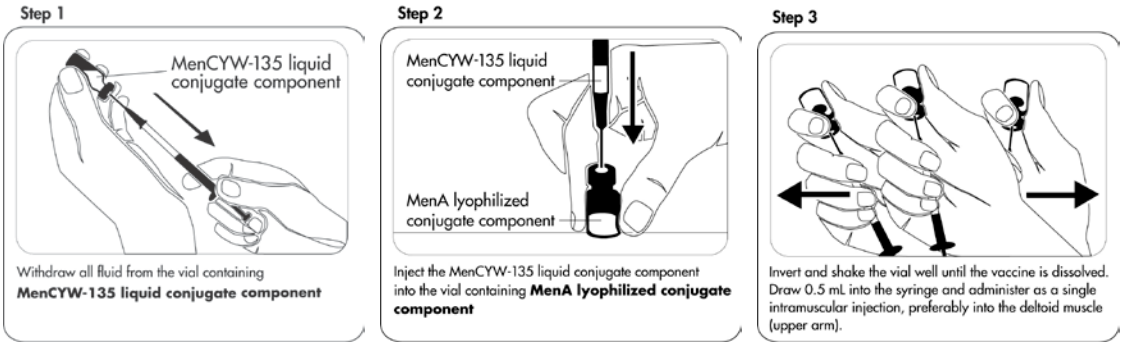
MENVEO does not prevent *N. meningitidis* serogroup B infections.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

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

Each dose of MENVEO should be administered as a single 0.5-mL intramuscular injection, preferably into the anterolateral aspect of the thigh in infants or into the deltoid muscle (upper

arm) in toddlers, adolescents, and adults. Do not administer MENVEO intravenously, subcutaneously, or intradermally.

2.3 Dosing Schedule

The dosing schedule for individuals initiating vaccination is as follows:

Infants 2 Months of Age

MENVEO is to be administered as a four-dose series at 2, 4, 6, and 12 months of age.

Children 7 Months through 23 Months of Age

MENVEO is to be administered as a two-dose series with the second dose administered in the second year of life and at least three months after the first dose.

Children 2 Years through 10 Years of Age

MENVEO is to be administered as a single dose. For children 2 years through 5 years of age at continued high risk of meningococcal disease, a second dose may be administered 2 months after the first dose.

Adolescents and Adults 11 Years through 55 Years of Age

MENVEO is to be administered as a single dose.

3 DOSAGE FORMS AND STRENGTHS

MENVEO is a solution for intramuscular injection supplied as a lyophilized MenA conjugate vaccine component to be reconstituted with the accompanying MenCYW-135 liquid conjugate vaccine component. A single dose, after reconstitution, is 0.5 mL. *[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 CRM_{197}-, 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 at least 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

Guillain-Barré syndrome (GBS) has been reported in temporal relationship following administration of another U.S.-licensed meningococcal quadrivalent polysaccharide conjugate vaccine. The decision to administer MENVEO to subjects with a known history of Guillain-Barré Syndrome should take into account the potential benefits and risks.

5.5 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including MENVEO, to an infant born prematurely should be based on consideration of the individual infant's medical status, and the potential benefits and possible risks of vaccination.

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.

Children 2 Months through 23 Months of Age

The safety of MENVEO in infants vaccinated at 2, 4, 6, and 12 months of age was evaluated in three randomized multicenter clinical studies[1-3] conducted in the U.S., Australia, Canada, Taiwan, and several countries of Latin America in which 8,735 infants received at least one dose of MENVEO and routine infant vaccines (diphtheria toxoid; acellular pertussis; tetanus toxoid; inactivated polio types 1, 2, and 3; hepatitis B; *Haemophilus influenzae* type b (Hib) antigens; pentavalent rotavirus; and 7-valent pneumococcal conjugate). With Dose 4 of MENVEO, toddlers received concomitantly the following vaccines: 7-valent pneumococcal conjugate; measles, mumps, rubella, and varicella; and inactivated hepatitis A. A total of 2,864 infants in these studies received the routine infant/toddler vaccines only. The infants who received MENVEO were Caucasian (33%), Hispanic (44%), African American (8%), Asian (8%), and other racial/ethnic groups (7%); 51% were male, with a mean age of 65.1 days (Standard Deviation [SD]: 7.5 days) at the time of first vaccination.

Safety data for administration of two doses of MENVEO in children between 6 through 23 months of age are available from three randomized studies[1,4,5] conducted in the U.S., Latin America, and Canada, of which one U.S. study specifically addressed the safety of MENVEO administered concomitantly with measles, mumps, rubella, and varicella vaccine (MMRV). The

1,985 older infants and toddlers who received two doses of MENVEO were Caucasian (49%), Hispanic (32%), African American (11%), and other racial/ethnic groups (8%), 51% male, with a mean age of 10.1 months (SD: 2.0 months).

Children 2 Years through 10 Years of Age

The safety of MENVEO in children 2 years through 10 years of age was evaluated in four clinical trials[6-9] conducted in North America (66%), Latin America (28%), and Europe (6%) in which 3,181 subjects received MENVEO and 2,116 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 = 1,255]). The subjects 2 years 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 years through 5 years of age.

Adolescents and Adults

The safety of MENVEO in individuals 11 through 55 years of age was evaluated in five randomized controlled clinical trials[10-14] in which 6,185 participants received MENVEO alone (5,286 participants), MENVEO concomitant with other vaccine(s) (899 participants), or a U.S.-licensed comparator vaccine (1,966 participants). In the concomitant trials[11,14] MENVEO was given with vaccines containing: tetanus toxoid, diphtheria toxoid and pertussis (Tdap), or Tdap with human papillomavirus (HPV). The comparator vaccine was either MENOMUNE (209 participants) or MENACTRA (1,757 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 Tdap or with Tdap plus HPV. Overall, subjects were Caucasian (50%), followed by Hispanic (40%), African American (7%), and other racial/ethnic groups (3%). Among recipients of MENVEO, 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).

In most trials, solicited local and systemic adverse reactions were monitored daily for 7 days following each (one or more) vaccination and recorded on a diary card. Participants were monitored for unsolicited adverse events which included adverse events requiring a physician visit or Emergency Department visit (i.e., medically-attended) or which led to a subject's withdrawal from the study. Among children, adolescents, and adults aged 2 years to 55 years, medically significant adverse events and serious adverse events (SAE) were monitored for 6 months after vaccination. Across the studies of infants and toddlers aged 2 months through 23

months, either all medically-attended or all medically-significant adverse events were collected in the period between the infant dose(s) and the toddler doses and during the 6-month period after the toddler dose.

Solicited Adverse Reactions

The reported frequencies of solicited local and systemic adverse reactions from U.S. infants in the largest multinational safety study of MENVEO[2] are presented in Table 1. Among the U.S. participants in the group receiving MENVEO with routine vaccines, 51% were female; 64% were Caucasian, 12% were African American, 15% were Hispanic, 2% were Asian, and 7% were of other racial/ethnic groups.

In infants initiating vaccination at 2 months of age and receiving the four-dose series, common solicited adverse reactions (≥10%) were tenderness (24% to 41%) and erythema at injection site (11% to 15%), irritability (42% to 57%), sleepiness (29% to 50%), persistent crying (21% to 41%), change in eating habits (17% to 23%), vomiting (5% to 11%), and diarrhea (8% to 16%). The rates of solicited adverse reactions reported for subjects aged 2 months and above receiving MENVEO with routine vaccines at 2, 4, 6 and 12 months of age were comparable to rates among subjects who only received routine vaccines.

Table 1: Rates of Solicited Adverse Reactions Reported in U.S. Infants, 2 Months of Age and Older, during the 7 Days following Each Vaccination with MENVEO Administered with Routine Infant/Toddler Vaccines, or Routine Infant/Toddler Vaccines Alone, at 2, 4, 6, and 12 Months of Age[a]

	Dose 1		**Dose 2**		**Dose 3**		**Dose 4**	
	MENVEO with Routine[b] %	**Routine Vaccines[b]** %	**MENVEO with Routine[b]** %	**Routine Vaccines[b]** %	**MENVEO with Routine[b]** %	**Routine Vaccines[b]** %	**MENVEO with Routine[b]** %	**Routine Vaccines[b]** %
Local Adverse Reactions[c]	**n = 1,250-1,252**	**n = 428**	**n = 1,205-1,207**	**n = 399**	**n = 1,056-1,058**	**n = 351-352**	**n = 1,054-1,055**	**n = 334-337**
Tenderness, any	41	45	31	36	24	32	29	39
Tenderness, severed	3	5	2	2	1	3	1	1
Erythema, any	11	14	12	21	14	23	15	25
Erythema, >50 mm	<1	<1	0	0	0	0	0	0
Induration, any	8	16	9	17	8	19	8	21
Induration, >50 mm	0	<1	0	0	0	0	0	0
Systemic Adverse Reactions	**n = 1,246-1,251**	**n = 427-428**	**n = 1,119-1,202**	**n = 396-398**	**n = 1,050-1,057**	**n = 349-350**	**n = 1,054-1,056**	**n = 333-337**
Irritability, any	57	59	48	46	42	38	43	42
Irritability, severe[e]	2	2	1	3	1	1	2	1
Sleepiness, any	50	50	37	36	30	30	29	27

Sleepiness, severe[f]	2	1	1	1	<1	<1	1	0
Persistent crying, any	41	38	28	24	22	17	21	18
Persistent crying, ≥3 hours	2	2	2	2	1	1	1	1
Change in eating habits, any	23	24	18	17	17	13	19	16
Change in eating habits, severe[g]	1	1	1	1	1	<1	1	0
Vomiting, any	11	9	7	6	6	4	5	4
Vomiting, severe[h]	<1	0	<1	0	<1	0	<1	0
Diarrhea, any	16	11	11	8	8	6	13	9
Diarrhea, severe[i]	<1	<1	<1	<1	1	<1	1	1
Rash[j]	3	3	3	4	3	3	4	3
Fever ≥38.°C[k]	3	2	4	6	7	6	9	7
Fever 38.0-38.9°C	3	2	4	5	7	6	6	5
Fever 39.0-39.9°C	0	0	1	1	<1	0	2	2
Fever ≥40.0°C	0	<1	0	<1	0	0	<1	0

Clinicaltrials.gov Identifier NCT00806195.[2]

n = Number of subjects who completed the diary card for a given symptom at the specified vaccination.

[a] As-Treated Safety Subpopulation = U.S. children who received at least one dose of study vaccine and whose diary cards were completed per protocol and returned to the site.

[b] Routine infant/toddler vaccines include DTaP-IPV-Hib and PCV7 at Doses 1, 2, 3, and PCV7, MMRV and Hepatitis A vaccines at Dose 4. HBV and rotavirus vaccines were allowed according to ACIP recommendations.

[c] Local reactogenicity of MENVEO and PCV7 was assessed.

[d] Tenderness, severe = Cried when injected limb moved.

[e] Irritability, severe = Unable to console.

[f] Sleepiness, severe = Sleeps most of the time, hard to arouse.

[g] Change in eating habits, severe = Missed >2 feeds.

[h] Vomiting, severe = Little/no intake for more prolonged time.

[i] Diarrhea, severe = ≥6 liquid stools, no solid consistency.

[j] Rash was assessed only as present or not present, without a grading for severity.

[k] Axillary temperature.

The safety of a second dose of MENVEO administered at 12 months of age concomitantly with MMRV was investigated in a randomized, controlled, multicenter study[5] conducted in the U.S. The rates of solicited adverse reactions reported were comparable between the concomitantly administered group (MENVEO with MMRV) and the group which received MMRV alone, or

MENVEO alone. The frequency and severity of solicited local and systemic reactions occurring within 7 days following vaccination at 12 months of age are shown in Table 2. In subjects who received both MENVEO and MMRV at 12 months of age local reactions at both injection sites were evaluated separately. Body temperature measurements were collected for 28 days following the 12-months-of-age visit, when MMRV was administered to the vaccinees. Common solicited adverse reactions (≥10%) among children initiating vaccination at 7 months through 23 months of age and receiving the two-dose series were tenderness (10% to 16%) and erythema at injection site (12% to 15%), irritability (27% to 40%), sleepiness (17% to 29%), persistent crying (12% to 21%), change in eating habits (12% to 20%), and diarrhea (10% to 16%). An examination of the fever profile during this period showed that MENVEO administered with MMRV did not increase the frequency or intensity of fever above that observed for the MMRV-only group.

Table 2: Rates of Solicited Adverse Reactions Reported in U.S. Toddlers during the 7 Days following Vaccination with MENVEO Administered at 7-9 Months and 12 Months of Age, MENVEO Administered Alone at 7-9 Months and with MMRV at 12 Months of Age, and MMRV Administered Alone at 12 Months of Age[a]

	MENVEO		**MENVEO + MMRV**		**MMRV**
	MENVEO 7-9 Months %	**MENVEO 12 Months %**	**MENVEO 7-9 Months %**	**MENVEO with MMRV 12 Months %**	**MMRV 12 Months %**
Local Adverse Reactions– MENVEO Site	**n = 460-462**	**n = 381-384**	**n = 430-434**	**n = 386-387**	
Tenderness, any	11	10	11	16	N/A
Tenderness, severe[b]	<1	<1	<1	0	N/A
Erythema, any	15	13	13	12	N/A
Erythema, >50 mm	<1	<1	0	1	N/A
Induration, any	8	8	7	8	N/A
Induration, >50 mm	<1	<1	0	1	N/A
Local Adverse Reactions– MMRV Site				**n = 382-383**	**n = 518-520**
Tenderness, any	N/A	N/A	N/A	16	19
Tenderness, severe[b]	N/A	N/A	N/A	0	<1
Erythema, any	N/A	N/A	N/A	15	14
Erythema, >50 mm	N/A	N/A	N/A	1	<1
Induration, any	N/A	N/A	N/A	13	8
Induration, >50 mm	N/A	N/A	N/A	<1	0
Systemic Adverse Reactions	**n = 461-463**	**n = 385-386**	**n = 430-434**	**n = 387-389**	**n = 522-524**
Irritability, any	40	27	37	37	44
Irritability, severe[c]	2	2	2	1	3
Sleepiness, any	26	17	29	26	32
Sleepiness, severe[d]	2	1	1	1	2
Persistent crying, any	21	12	20	19	20
Persistent crying, ≥3 hours	2	1	1	1	2
Change in eating habits, any	17	12	17	20	20

Change in eating habits, severe[e]	<1	1	1	2	1
Vomiting, any	9	6	9	6	6
Vomiting, severe[f]	<1	<1	<1	<1	<1
Diarrhea, any	16	10	15	15	20
Diarrhea, severe[g]	2	1	<1	1	2
Rash[h]	3	5	6	6	8
Fever ≥38.0°C[i]	5	5	6	9	7
Fever 38.0-38.9°C	3	3	5	7	7
Fever 39.0-39.9°C	2	2	1	1	1
Fever ≥40.0°C	<1	1	<1	<1	0

Clinicaltrials.gov Identifier NCT00626327[5].

n = Number of subjects who completed the diary card for a given symptom at the specified vaccination.

[a] As-Treated Safety Subpopulation = U.S. children who received at least one dose of study vaccine and whose diary cards were completed per protocol and returned to the site.

[b] Tenderness, severe = Cried when injected limb moved.

[c] Irritability, severe = Unable to console.

[d] Sleepiness, severe = Sleeps most of the time, hard to arouse.

[e] Change in eating habits, severe = Missed >2 feeds.

[f] Vomiting, severe = Little/no intake for more prolonged time.

[g] Diarrhea, severe = ≥6 liquid stools, no solid consistency.

[h] Rash was assessed only as present or not present, without a grading for severity.

[i] Axillary temperature.

In clinical trials of children 2 years through 10 years of age,[6-9] the most frequently occurring adverse reactions (≥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 years through 55 years of age, the most frequently occurring adverse reactions (≥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 years through 5 years and 6 years through 10 years of age who received a single dose of MENVEO or MENACTRA in a randomized controlled, multicenter study[9] conducted in the U.S. and Canada are shown in Table 3. Following a second dose of MENVEO administered to children 2 years through 5 years of age, the most common solicited adverse reactions (≥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[12] are provided in Tables 4 and 5, respectively. In neither study were concomitant vaccines administered with the study vaccines.

Table 3: Rates of Solicited Adverse Reactions within 7 Days following a Single Vaccination in Children 2 Years through 5 Years and 6 Years through 10 Years of Age

Participants 2 through 5 Years of Age

	MENVEO n = 693 %			MENACTRA n = 684 %		
Local Adverse Reaction	**Any**	**Moderate**	**Severe**	**Any**	**Moderate**	**Severe**
Injection site pain[a]	33	6	1	35	8	0.4
Erythema[b]	27	5	1	25	3	0.3
Induration[b]	18	2	0.4	18	2	0.3
Systemic Adverse Reaction[e]						
Irritability[a]	21	6	1	22	7	1
Sleepiness[a]	16	3	1	18	5	1
Change in eating[a]	9	2	1	10	2	0.3
Diarrhea[a]	7	1	0.1	8	1	0
Headache[a]	5	1	0	6	1	0.3
Rash[c]	4	-	-	5	-	-
Arthralgia[a]	3	1	0.1	4	1	0
Vomiting[a]	3	1	0.1	3	1	0
Fever[d]	2	0.4	0	2	0.3	0

Participants 6 through 10 Years of Age

	MENVEO n = 582 %			MENACTRA n = 571 %		
Local Adverse Reaction	**Any**	**Moderate**	**Severe**	**Any**	**Moderate**	**Severe**
Injection site pain[a]	39	8	1	45	10	2
Erythema[b]	28	5	1	22	2	0.2
Induration[b]	17	2	0.3	13	2	0
Systemic Adverse Reaction[e]						
Headache[a]	18	3	1	13	2	1
Malaise[a]	14	3	1	11	3	1
Myalgia[a]	10	2	1	10	2	1
Nausea[a]	8	2	1	6	2	0.4
Arthralgia[a]	6	1	0	4	1	0.4
Chills[a]	5	1	0	5	1	0.4
Rash[c]	5	-	-	3	-	-
Fever[d]	2	1	0	2	0	0.4

Clinicaltrials.gov Identifier NCT00616421.[9]

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

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

[c] Rash was assessed only as present or not present, without a grading for severity.

[d] Fever grading: 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.

[e] Different systemic reactions were solicited in different age groups.

Table 4: Rates of Solicited Adverse Reactions within 7 Days following Vaccination in Individuals 11 Years through 18 Years of Age

Local Adverse Reaction	**MENVEO n = 1,631 %**			**MENACTRA n = 539 %**		
	Any	**Moderate**	**Severe**	**Any**	**Moderate**	**Severe**
Injection site pain[a]	44	9	1	53	11	1
Erythema[b]	15	2	0.4	16	1	0
Induration[b]	12	2	0.2	11	1	0
Systemic Adverse Reaction						
Headache[a]	29	8	2	28	7	1
Myalgia[a]	19	4	1	18	5	0.4
Nausea[a]	12	3	1	9	2	1
Malaise[a]	11	3	1	12	5	1
Chills[a]	8	2	1	7	1	0.2
Arthralgia[a]	8	2	0.4	6	1	0
Rash[c]	3	-	-	3	-	-
Fever[d]	1	0.4	0	1	0	0

Clinicaltrials.gov Identifier NCT00450437.[12]

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

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

[c] Rash was assessed only as present or not present, without a grading for severity.

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

Table 5: Rates of Solicited Adverse Reactions within 7 Days following Vaccination in Individuals 19 Years through 55 Years of Age

Local Adverse Reaction	**MENVEO n = 1,018**	**MENACTRA n = 336**

	%			%		
	Any	**Moderate**	**Severe**	**Any**	**Moderate**	**Severe**
Injection site pain[a]	38	7	0.3	41	6	0
Erythema[b]	16	2	1	12	1	0
Induration[b]	13	1	0.4	9	0.3	0
Systemic Adverse Reaction						
Headache[a]	25	7	2	25	7	1
Myalgia[a]	14	4	0.5	15	3	1
Malaise[a]	10	3	1	10	2	1
Nausea[a]	7	2	0.4	5	1	0.3
Arthralgia[a]	6	2	0.4	6	1	1
Chills[a]	4	1	0.1	4	1	0
Rash[c]	2	-	-	1	-	-
Fever[d]	1	0.3	0	1	0.3	0

Clinicaltrials.gov Identifier NCT00450437.[12]

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

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

[c] Rash was assessed only as present or not present, without a grading for severity.

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

Solicited Adverse Reactions following Concomitant Vaccine Administration

The safety of 4-dose series of MENVEO administered concomitantly with U.S.-licensed routine infant and toddler vaccines was evaluated in one pivotal trial[2]. The safety of a 2-dose series of MENVEO initiated at 7-9 months of age, with the second dose administered concomitantly with U.S.-licensed MMR and V vaccine at 12 months of age, was evaluated in one pivotal trial.[5] Rates of solicited adverse reactions which occurred 7 days following vaccination are shown in Tables 1 and 2, respectively. There was no significant increase in the rates of solicited systemic or local reactions observed in recipients of routine childhood vaccines when concomitantly vaccinated with MENVEO. *[*See *Concomitant Administration with Other Vaccines (7.1).]*

The safety of MENVEO administered concomitantly with Tdap and HPV was evaluated in a single center study[14] conducted in Costa Rica. Solicited local and systemic adverse reactions were reported as noted above. In this study, subjects 11 through 18 years of age received MENVEO concomitantly with Tdap and HPV (n = 540), or MENVEO followed one month later by Tdap and then one month later by HPV (n = 541), or Tdap followed one month later by MENVEO and then one month later by HPV (n = 539). Some solicited systemic adverse reactions were more frequently reported in the group that received MENVEO, Tdap, and HPV

concomitantly, (headache 40%, malaise 25%, myalgia 27%, and arthralgia 17%) compared with 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 Tdap), 36% reported headache, 20% malaise, and 16% myalgia. Among subjects administered MENVEO one month after Tdap, 27% reported headache, 18% malaise, and 16% myalgia.

Serious Adverse Events in All Safety Studies

Serious adverse events in subjects receiving a four-dose series of MENVEO at 2, 4, 6, and 12 months were evaluated in three randomized multicenter clinical studies.[1-3] In the two controlled studies,[2,3] the proportions of infants randomized to receive the four-dose series of MENVEO concomitantly with routine vaccinations and infants who received routine vaccinations alone that reported serious adverse events during different study periods were, respectively: a) 2.7% and 2.2%, during the infant series; b) 2.5% and 2.5%, between the infant series and the toddler dose; c) 0.3% and 0.3%, in the one month following the toddler dose; and d) 1.6% and 2.2%, during the 6-month follow-up period after the last dose. In the third study,[1] which was controlled up to the toddler dose, the proportions of infants randomized to dosing regimens that included receiving four doses of MENVEO concomitantly with routine vaccinations at 2, 4, 6, and 12 months and infants who received routine vaccinations alone that reported serious adverse events during different study periods were, respectively: a) 3.5% and 3.6%, during the infant series; and b) 2.8% and 3.3%, between the infant series and the toddler dose; and c) 0.5% and 0.7%, in the one month following the toddler dose. In the same study, 1.9% of infants randomized to receive the four-dose series of MENVEO concomitantly with routine vaccinations reported serious adverse events during the 6-month follow-up period after the toddler dose. The most common serious adverse events reported in these three studies were wheezing, pneumonia, gastroenteritis, and convulsions, and most occurred at highest frequency after the infant series.

In a study of older infants[5] randomized to receive the two-dose series of MENVEO concomitantly with MMRV at 12 months of age, the rates of serious adverse events during the study, including the 6-month follow-up period after the last dose, were 3.6% and 3.8%, for the groups receiving MENVEO with MMRV and MENVEO only, respectively. Infants receiving MMRV alone, who had a shorter period of study participation as they were enrolled at 12 months of age, had a lower rate of serious adverse events (1.5%). Among 1,597 study subjects included in the safety population, the most commonly reported serious adverse events in all study arms combined were dehydration (0.4%) and gastroenteritis (0.3%). Across the submitted studies of individuals 2 through 23 months of age, within 28 days of vaccination, two deaths were reported in the groups receiving MENVEO (one case of sudden death and one case of sepsis), while no deaths were reported in the control group. None of the deaths was assessed as related to vaccination. Among subjects with symptom onset within 42 days of vaccination (Days 12, 25, 29), 3/12,049 [0.02%, 95% CI: (0.01%, 0.07%)] recipients of MENVEO and 0/2,877 [0%, 95% CI: (0%, 0.13%)] control recipients were diagnosed with Kawasaki Disease. One case of acute disseminated encephalomyelitis with symptom onset 29 days post-Dose 4 was observed

in a participant given MENVEO coadministered with routine U.S. childhood vaccines at 12 months of age (including MMR and varicella vaccines).

The information regarding serious adverse events in subjects 2 years through 10 years of age was derived from 3 randomized, controlled clinical trials.[7-9] Safety follow-up ranged from 6 months through 12 months and included 2,883 subjects administered MENVEO. Serious adverse events reported during the safety follow-up periods occurred in 21/2,883 (0.7%) of subjects receiving MENVEO, in 7/1,255 (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 1,255 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 (6/2,883 [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,[6] 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 years through 55 years of age was derived from 5 randomized, controlled clinical trials.[10-14] Serious adverse events reported within 6 months of vaccination occurred in 40/6,185 (0.6%) of subjects receiving MENVEO, 13/1,757 (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 6,185 (0.1%) subjects in the group receiving MENVEO, 4 of 1,757 (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.

Postmarketing Observational Safety Study

In a postmarketing observational safety study conducted in a United States health maintenance organization, data from electronic health records of 48,899 persons 11 through 21 years of age were used to evaluate pre-specified events of interest following vaccination with MENVEO. Using a self-controlled case series method, Bell's palsy showed a statistically significant increased risk in the period 1 to 84 days post vaccination compared with the control period, with

an overall adjusted relative incidence of 2.9 (95% CI: 1.1-7.5). Among the 8 reported cases of Bell's palsy, 6 cases occurred in persons who received MENVEO concomitantly with one or more of the following vaccines: Tdap, HPV, and Influenza vaccine. All reported Bell's palsy cases resolved.

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.

In two clinical trials of infants initiating vaccination at 2 months of age,[1,3] MENVEO was given concomitantly at 2, 4, and 6 months with routine infant vaccines: diphtheria toxoid; acellular pertussis; tetanus toxoid; inactivated polio types 1, 2, and 3; hepatitis B; *Haemophilus influenzae* type b (Hib) antigens; pentavalent rotavirus; and 7-valent pneumococcal conjugate vaccine. For Dose 4 given at 12 months of age, MENVEO was given concomitantly with the following vaccines: 7-valent pneumococcal conjugate, MMRV or MMR+V, and inactivated hepatitis A. In a clinical trial of older infants (≥7 months of age) and toddlers,[5] MENVEO was administered concomitantly with MMRV or MMR+V vaccine(s) at 12 months of age. No immune interference was observed for the concomitantly administered vaccines, including most pneumococcal vaccine serotypes (post-Dose 3); no immune interference was observed post-Dose 4 for any pneumococcal vaccine serotypes.[1,3] *[*See *Immunogenicity of Concomitantly Administered Vaccines (14.5).]*

For children 2 years 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,[14] MENVEO was given concomitantly with the following: Tdap and HPV; no interference was observed in meningococcal immune responses when compared with 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 Tdap and HPV as compared with Tdap alone. *[*See *Immunogenicity of Concomitantly Administered Vaccines (14.5).]*

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 5,065 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 3,952 recipients of MENVEO (7 spontaneous abortions, no congenital anomalies). Six pregnancies occurred among 1,113 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

GlaxoSmithKline maintains a surveillance registry to collect data on pregnancy outcomes and newborn health status outcomes following exposure to MENVEO during pregnancy. Women who receive MENVEO during pregnancy should be encouraged to contact GlaxoSmithKline directly or their healthcare provider should contact GlaxoSmithKline by calling 1-877-413-4759.

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 breastfed child.

8.4 Pediatric Populations

Safety and effectiveness of MENVEO in children under 2 months of age 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 CRM_{197} Conjugate Vaccine] is a sterile liquid vaccine administered by intramuscular injection that contains *N. meningitidis* serogroup A, C, Y, and W-135 oligosaccharides conjugated individually to *Corynebacterium diphtheriae* CRM_{197} 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 (CRM_{197}) 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 CRM_{197} 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 mcg MenA oligosaccharide, 5 mcg of each of MenC, MenY, and MenW-135 oligosaccharides and 32.7 to 64.1 mcg CRM_{197} protein. Residual formaldehyde per dose is estimated to be not more than 0.30 mcg.

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.[16] 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

For all age groups, effectiveness has been inferred from the measurement of serogroup-specific anticapsular antibodies with bactericidal activity using pooled human serum that lacked bactericidal activity as the source of exogenous complement (hSBA). In the absence of a licensed comparator vaccine for use in infants, the pre-specified endpoint for effectiveness of MENVEO in U.S. infants receiving a four- dose series at 2, 4, 6, and 12 months of age was the proportion of subjects achieving an hSBA ≥1:8, with the lower limit of the 2-sided 95% CI for the point estimate being ≥80% of vaccinees for serogroup A, and ≥85% of vaccinees for serogroups C, W-135, and Y one month following the final dose.

The effectiveness of MENVEO in subjects 2 years through 55 years of age was assessed by comparing the hSBA responses to immunization with MENVEO to those following immunization with the licensed meningococcal quadrivalent conjugate vaccine MENACTRA.

The primary effectiveness endpoint was hSBA seroresponse to each serogroup 28 days after vaccination. Seroresponse was defined as: a) post-vaccination hSBA ≥1:8 for subjects with a baseline hSBA <1:4; or, b) at least 4-fold higher than baseline titers for subjects with a pre-vaccination hSBA ≥1:4. Secondary endpoints included the proportion of subjects with post-vaccination hSBA ≥1:8 and the hSBA Geometric Mean Titer (GMT) for each serogroup. In a separate group of children 2 years through 5 years of age randomized to receive two doses of MENVEO administered two months apart, seroresponse rate, proportion with post-vaccination hSBA ≥1:8 and GMT were determined for each serogroup.

14.1 Immunogenicity in Infants

The effectiveness of MENVEO in infants was assessed in a randomized, controlled, multicenter study.[3] Among the subjects receiving MENVEO who were included in the per-protocol analysis,

the mean age at enrollment was 65 days; 51% were male; 67% were Caucasian, 6% were African American, 15% were Hispanic, 2% were Asian, and 9% were noted as other racial/ethnic groups. The pre-defined criteria for immunogenicity were met for all four serogroups A, C, W-135, and Y at one month following completion of a four-dose series at 2, 4, 6, and 12 months of age (Table 6).

The percentage of subjects with hSBA ≥1:8 at 7 months was 94% to 98% for serogroups C, W-135, and Y and 76% for serogroup A.

Table 6: Bactericidal Antibody Responses following Administration of MENVEO with Routine Infant/Toddler Vaccines at 2, 4, 6, and 12 Months of Age

Serogroup		Post 3rd Dose	Post 4th Dose
		n = 202	**n = 168**
A	% ≥1:8 95% CI	76 (69, 81)	89 (83[a], 93)
	GMT 95% CI	21 (17, 26)	54 (44, 67)
		n = 199	**n = 156**
C	% ≥1:8 95% CI	94 (90, 97)	95 (90[a], 98)
	GMT 95% CI	74 (62, 87)	135 (107, 171)
		n = 194	**= 153**
W-135	% ≥1:8 95% CI	98 (95, 99)	97 (93[a], 99)
	GMT 95% CI	79 (67, 92)	215 (167, 227)
		n = 188	**n = 153**
Y	% ≥1:8 n5% CI	94 (89, 97)	96 (92[a], 99)
	GMT 95% CI	51 (43, 61)	185 (148, 233)

Clinicaltrials.gov Identifier NCT01000311.[3]

%≥1:8 = Proportions of subjects with hSBA ≥1:8 against a given serogroup; CI = Confidence interval; GMT = Geometric mean antibody titer; n = Number of infants eligible for inclusion in the Per-Protocol Immunogenicity population for whom serological results were available for the post-Dose 3 and post-Dose 4 evaluations.

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

[a] Pre-specified criteria for adequacy of immune response were met (LL of the 95% CI >80% for serogroup A and >85% for serogroups C, W, and Y).

The effectiveness of two doses of MENVEO given at 7-9 months and 12 months of age was assessed in a randomized, multicenter, controlled clinical trial[5] conducted in the U.S. This study also investigated the concomitant administration of MENVEO and MMRV. The per-protocol population for assessing the response to two doses of MENVEO consisted of 386 subjects. Among subjects who completed the per-protocol analysis, their mean age at enrollment was 8.5 months (SD: 0.8 months); they were 50% male; 61% were Caucasian, 15% were Hispanic, 10% were African American, 4% were Asian, and 10% were noted as other racial/ethnic groups.

Among the per-protocol population, after MENVEO administered at 7-9 and at 12 months, the proportions of subjects with hSBA ≥1:8 for serogroups A, C, W-135, and Y were respectively: 88% (84-91), 100% (98-100), 98% (96-100), 96% (93-99).

14.2 Immunogenicity in Children

Effectiveness in subjects 2 years through 10 years of age was evaluated in a randomized, multicenter, active-controlled clinical study[9] comparing hSBA responses following one dose of MENVEO or MENACTRA. The study was conducted in the U.S. and Canada and was stratified by age (2 years through 5 years and 6 years through 10 years). The per-protocol population evaluated after a single dose of vaccine consisted of 1,170 subjects who received MENVEO and 1,161 who received MENACTRA (see Table 7) and included serological results for 89% to 95% of subjects, depending on serogroup and age group. Demographics for the 616 and 619 subjects 2 through 5 years of age for MENVEO and MENACTRA were as follows: 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 racial/ethnic groups. Demographics were for 554 and 542 per-protocol subjects 6 through 10 years of age for MENVEO and MENACTRA were as follows: 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 racial/ethnic groups. In a separate group of children 2 years through 5 years of age randomized to receive two doses of MENVEO administered two months apart, the per-protocol population evaluated after two doses of MENVEO consisted of 297 subjects and included serologic results for 96% to 99% of subjects, depending on serogroup.

In study participants 2 years through 5 years and 6 years 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 7).

Table 7: Comparison of Bactericidal Antibody Responses[a] to MENVEO and MENACTRA 28 Days after Vaccination of Subjects 2 Years through 5 Years and 6 Years through 10 Years of Age

	2-5 Years			6-10 Years		
Endpoint by Serogroup	**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[b]	72 (68, 75)	77 (73, 80)	-5 (-10, -0)[c]	77 (73, 80)	83 (79, 86)	-6 (-11, -1)[c]
% ≥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[b]	60 (56, 64)	56 (52, 60)	4 (-2, 9)[d]	63 (59, 67)	57 (53, 62)	6 (0, 11)[d]
% ≥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[b]	72 (68, 75)	58 (54, 62)	14 (9, 19)[d]	57 (53, 61)	44 (40, 49)	13 (7, 18)[d]
% ≥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[b]	66 (62, 70)	45 (41, 49)	21 (16, 27)[d]	58 (54, 62)	39 (35, 44)	19 (13, 24)[d]
% ≥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)

Clinicaltrials.gov Identifier NCT00616421.[9]

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

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

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

[d] 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 years 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 ≥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.

14.3 Immunogenicity in Adolescents

Effectiveness in subjects 11 through 55 years of age was evaluated in a randomized, multicenter, active-controlled clinical study[12] comparing the hSBA responses following one dose of MENVEO or MENACTRA. The study was 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 3,539 participants, who were randomized to receive a dose of MENVEO (n = 2,663) or MENACTRA (n = 876). Among subjects who completed the per-protocol evaluation for immunogenicity (n = 3,393, MENVEO = 2,549, MENACTRA = 844), demographics for subjects receiving MENVEO and MENACTRA respectively were as follows: 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 racial/ethnic groups. Immunogenicity for each serogroup was assessed in a subset of study participants (see Tables 8 and 10).

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 8).

Table 8: Comparison of Bactericidal Antibody Responses[a] to MENVEO and MENACTRA 28 Days after Vaccination of Subjects 11 through 18 Years of Age

	Bactericidal Antibody Response[a]		**Comparison of MENVEO and MENACTRA**	
Endpoint by Serogroup	**MENVEO (95% CI)**	**MENACTRA (95% CI)**	**MENVEO/ MENACTRA (95% CI)**	**MENVEO minus MENACTRA (95% CI)**
A	**n = 1,075**	**n = 359**		

% Seroresponse[b]	75 (72, 77)	66 (61, 71)		8 (3, 14)[c]
% ≥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 = 1,396**	**n = 460**		
% Seroresponse[b]	76 (73, 78)	73 (69, 77)		2 (-2, 7)[c]
% ≥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 = 1,024**	**n = 288**		
% Seroresponse[b]	75 (72, 77)	63 (57, 68)		12 (6, 18)[c]
% ≥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 = 1,036**	**n = 294**		
% Seroresponse[b]	68 (65, 71)	41 (35, 47)		27 (20, 33)[c]
% ≥1:8	88 (85, 90)	69 (63, 74)	-	19 (14, 25)
GMT	51 (42, 61)	18 (14, 23)	2.82 (2.26, 3.52)	-

Clinicaltrials.gov Identifier NCT00450437.[12]

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

[b] 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.

[c] 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 9.

Table 9: Persistence of Immune Responses through 21 Months Post Vaccination among Adolescents Vaccinated with One Dose of MENVEO or MENACTRA

	% hSBA ≥1:8 (95% CI)			hSBA GMTs (95% CI)		
Serogroup	**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)

Clinicaltrials.gov Identifier NCT00856297.[15]

14.4 Immunogenicity in Adults

The study in subjects 11 through 55 years of age was a randomized, multicenter, active-controlled clinical trial[12] conducted in the U.S. and stratified by age (11 through 18 years of age and 19 through 55 years of age) as described above. *[*See *Immunogenicity in Adolescents (14.3).]*

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 10).

Table 10: Comparison of Bactericidal Antibody Responses to MENVEO and MENACTRA 28 Days after Vaccination of Subjects 19 through 55 Years of Age

	Bactericidal Antibody Response[a]		Comparison of MENVEO and MENACTRA	
Endpoint by Serogroup	**MENVEO (95% CI)**	**MENACTRA (95% CI)**	**MENVEO/ MENACTRA (95% CI)**	**MENVEO minus MENACTRA (95% CI)**
A	**n = 963**	**n = 321**		
%	67	68		-1

Seroresponse[b]	(64, 70)	(63, 73)		(-7, 5)[c]
% ≥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[b]	68 (64, 71)	60 (54, 65)		8 (2, 14)[c]
% ≥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[b]	50 (46, 55)	41 (35, 47)		9 (2, 17)[c]
% ≥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[b]	56 (51, 60)	40 (34, 46)		16 (9, 23)[c]
% ≥1:8	79 (76, 83)	70 (65, 75)	-	9 (3, 15)
GMT	44 (37, 52)	21 (17, 26)	2.10 (1.60, 2.75)	-

Clinicaltrials.gov Identifier NCT00450437[12].

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

[b] 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.

[c] 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]).

14.5 Immunogenicity of Concomitantly Administered Vaccines

In U.S. infants[1,3] who received MENVEO concomitantly with DTaP-IPV-Hib and PCV7 at 2, 4, and 6 months of age and HBV administered according to ACIP recommendations, there was no evidence for reduced antibody response to pertussis antigens (GMC to pertussis toxin, filamentous hemagglutinin, fimbriae, and pertactin), diphtheria toxoid (antibody levels ≥0.1 IU/mL), tetanus toxoid (antibody levels ≥0.1 IU/mL), poliovirus types 1, 2, and 3 (neutralizing

antibody levels ≥1:8 to each virus), *Haemophilus influenzae* type b (anti-PRP antibody ≥0.15mcg/mL), hepatitis B (anti-hepatitis B surface antigen ≥10 mIU/mL), or most serotypes of PCV7 (antibody levels ≥0.35 mcg/mL) relative to the response in infants administered DTaP-IPV-Hib, PCV7, and HBV. The immune responses to DTaP-IPV-Hib, PCV7, and HBV were evaluated one month following Dose 3.[1,3] No interference was observed for pertussis based on GMC ratios, or for the other concomitantly administered vaccines, with the exception of pneumococcal serotype 6B[1,3] and 23F[3], for which interference was suggested post-Dose 3. No interference was observed post-Dose 4 for these serotypes.[1,3]

There was no evidence for interference in the immune response to MMR and varicella vaccines (among initially seronegative children) in terms of percentages of children with anti-measles antibodies ≥255 mIU/mL, anti-mumps ≥10 ELISA antibody units, anti-rubella ≥10 IU/mL, and anti-varicella ≥5 gp ELISA units/mL, administered at 12 months of age[5] concomitantly with MENVEO relative to these vaccines administered alone. The immune responses to MMR and varicella vaccines were evaluated 6 weeks post vaccination.

For children 2 years 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 Tdap and HPV was evaluated in a study[14] 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 Tdap plus HPV (n = 540); MENVEO alone (n = 541); Tdap 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 antigens of MENVEO, the proportion (95% CI) of subjects achieving an hSBA seroresponse among those who received MENVEO plus Tdap plus HPV 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 Tdap plus MENVEO plus HPV, compared with Tdap 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 Tdap plus MENVEO plus HPV, compared with Tdap 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. 1,197 (1,061, 1,350) 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

All NCT numbers are as noted in the National Library of Medicine clinical trial database (see clinicaltrial.gov).

1. NCT00474526 (V59P14).
2. NCT00806195 (V59P23).
3. NCT01000311 (V59_33).
4. NCT00310856 (V59P9).
5. NCT00626327 (V59P21).
6. NCT00310817 (V59P7).
7. NCT00262028 (V59P8).
8. NCT00329849 (V59P10).
9. NCT00616421 (V59P20).
10. NCT01018732 (V59P6).
11. NCT00329901 (V59P11).
12. NCT00450437 (V59P13).
13. NCT00474487 (V59P17).
14. NCT00518180 (V59P18).
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16. 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

Product presentation for MENVEO is listed in Table 11 below. The container closures (synthetic rubber stoppers) do not contain latex.

Table 11: Product Presentation for MENVEO

Presentation	Carton NDC Number	Components
Five doses (10 vials) per package	58160-955-09	• 5 vials containing MenA lyophilized conjugate component [NDC 58160-958-01] • 5 vials containing MenCYW-135 liquid conjugate component [NDC 58160-959-01]

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.
- The importance of completing the immunization series.
- 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 GlaxoSmithKline pregnancy registry, as appropriate.

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