AHFS Category: 80:12

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Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine Menactra®

MCV4

℞ only

FOR INTRAMUSCULAR INJECTION

DESCRIPTION

Menactra®, Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine, is a sterile, intramuscularly administered vaccine that contains *Neisseria meningitidis* serogroup A, C, Y and W-135 capsular polysaccharide antigens individually conjugated to diphtheria toxoid protein. *N meningitidis* A, C, Y and W-135 strains are cultured on Mueller Hinton agar[1] and grown in Watson Scherp[2] media. The polysaccharides are extracted from the *N meningitidis* cells and purified by centrifugation, detergent precipitation, alcohol precipitation, solvent extraction and diafiltration. To prepare the polysaccharides for conjugation, they are depolymerized, derivatized, and purified by diafiltration. *Corynebacterium diphtheriae* cultures are grown in a modified Mueller and Miller medium[3] and detoxified with formaldehyde. The diphtheria toxoid protein is purified by ammonium sulfate fractionation and diafiltration. The derivatized polysaccharides are covalently linked to diphtheria toxoid and purified by serial diafiltration. The four meningococcal components, present as individual serogroup-specific glycoconjugates, compose the final formulated vaccine. No preservative or adjuvant is added during manufacture. Potency of Menactra vaccine is determined by quantifying the amount of each polysaccharide antigen that is conjugated to diphtheria toxoid protein and the amount of unconjugated polysaccharide present.

Menactra vaccine is manufactured as a sterile, clear to slightly turbid liquid. Each 0.5 mL dose of vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution to contain 4 µg each of meningococcal A, C, Y, and W-135 polysaccharides conjugated to approximately 48 µg of diphtheria toxoid protein carrier.

CLINICAL PHARMACOLOGY

Background

The meningococcus bacterium, *N meningitidis*, causes both endemic and epidemic disease, principally meningitis and meningococcemia. At least 13 meningococcal serogroups have been identified based on antigenic differences in their capsular polysaccharides. Five serogroups (A, B, C, Y and W-135) are responsible for nearly all cases of meningococcal disease worldwide.[4,5] Early clinical manifestations of meningococcal disease are often difficult to distinguish from other, more common but less serious illnesses.[6] Onset and progression of disease can be rapid; in most cases (60%), infected individuals are symptomatic for less than 24 hours before seeking medical care. Even with administration of appropriate antimicrobials and other adjunctive therapies, the case-fatality rate has remained at approximately 10%.[6,7,8,9] In cases of fulminant septicemia, the case fatality rate may reach 40%.[6] Approximately 11-19%[5] of meningococcal disease survivors have sequelae such as hearing loss and neurologic disability, or loss of skin, digits or limbs as a result of ischemia.

Mechanism of Action

The presence of bactericidal anti-capsular meningococcal antibodies has been associated with protection from invasive meningococcal disease.[10,11] Menactra vaccine induces the production of bactericidal antibodies specific to the capsular polysaccharides of serogroups A, C, Y and W-135.

Clinical Studies

Vaccine efficacy was inferred from the demonstration of immunologic equivalence to a US-licensed meningococcal polysaccharide vaccine, Menomune®–A/C/Y/W-135, Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined as assessed by Serum Bactericidal Assay (SBA). The SBA used to test sera contained an exogenous complement source that was either human (SBA-H) or, when correlated to SBA-H, baby rabbit (SBA-BR).[12]

The response to vaccination in children 2–10 years old was evaluated by the proportion of subjects having an SBA-H antibody titer of 1:8 or greater, for each serogroup. In adolescents and adults, the response to vaccination was evaluated by the proportion of subjects with a 4-fold or greater increase in bactericidal antibody to each serogroup as measured by SBA-BR.

Immunogenicity was evaluated in three comparative, randomized, US, multi-center, active controlled clinical trials that enrolled children (2–10 years old), adolescents (11–18 years old), and adults (18–55 years old). Participants received a dose of Menactra vaccine (N=2526) or Menomune–A/C/Y/W-135 vaccine (N=2317). For all age groups studied, sera were obtained before and approximately 28 days after vaccination. (Blinding procedures for safety assessments are described in **ADVERSE REACTIONS** section.)

In each of the trials, there were no substantive differences in demographic characteristics between the vaccine groups, between immunogenicity subsets or the overall study population. In the study of children 2–10 years old, the median age of participants was 3 years old; 95% completed the study. In the adolescent trial, the median age for both groups was 14 years; 99% completed the study. In the adult trial, the median age for both groups was 24 years; 94% completed the study.

Immunogenicity in Children

Of 1408 enrolled children 2–10 years old, immune responses evaluated in a subset of Menactra vaccine participants (2–3 years old, n=52; 4–10 years old, n=84) and Menomune–A/C/Y/W-135 vaccine participants (2–3 years old, n=53; 4–10 years old, n=84) were comparable for all four serogroups (**Table 1** and **Table 2**).

Table 1: Comparison of Bactericidal Antibody Responses* to Menactra vaccine and Menomune–A/C/Y/W-135 vaccine 28 Days After Vaccination for a Subset of Participants Aged 2–3 Years

		Menactra vaccine N‡=48-52		Menomune–A/C/Y/W-135 vaccine N‡=50-53	
Serogroup			**(95% CI)§**		**(95% CI)§**
A	% ≥1:8†	73	59,84	64	50,77
	GMT	10	8,13	10	7,12
C	% ≥1:8†	63	48,76	38	25,53
	GMT	27	14,52	11	5,21
Y	% ≥1:8†	88	75,95	73	59,84
	GMT	51	31,84	18	11,27
W-135	% ≥1:8†	63	47,76	33	20,47
	GMT	15	9,25	5	3,6

* Serum Bactericidal Assay with an exogenous human complement (SBA-H) source.
† The proportion of participants achieving at least an SBA-H titer of 1:8 was assessed using a 10% non-inferiority margin and a one-sided Type I error rate of 0.025.
‡ N = Number of subset participants with at least one valid serology result at Day 0 and Day 28.
§ The 95% CI for the Geometric Mean Titer (GMT) was calculated based on an approximation to the normal distribution.

Table 2: Comparison of Bactericidal Antibody Responses* to Menactra vaccine and Menomune–A/C/Y/W-135 vaccine 28 Days After Vaccination for a subset of Participants Aged 4–10 Years

		Menactra vaccine N‡=84		Menomune–A/C/Y/W-135 vaccine N‡=84	
Serogroup			**(95% CI)§**		**(95% CI)§**
A	% ≥1:8†	81	71,89	55	44,66
	GMT	19	14,26	7	6,9
C	% ≥1:8†	79	68,87	48	37,59
	GMT	28	19,41	12	7,18
Y	% ≥1:8†	99	94,100	92	84,97
	GMT	99	75,132	46	33,66
W-135	% ≥1:8†	85	75,92	79	68,87
	GMT	24	18,33	20	14,27

* Serum Bactericidal Assay with an exogenous human complement (SBA-H) source.
† The proportion of participants achieving at least an SBA-H titer of 1:8 was assessed using a 10% non-inferiority margin and a one-sided Type I error rate of 0.025.
‡ N = Number of subset participants with at least one valid serology result at Day 0 and Day 28.
§ The 95% CI for the Geometric Mean Titer (GMT) was calculated based on an approximation to the normal distribution.

In the subset of participants 2–3 years of age with undetectable pre-vaccination titers (ie, <4 at Day 0), seroconversion rates (defined as ≥8 at Day 28) were similar between the Menactra vaccine and Menomune–A/C/Y/W-135 vaccine recipients. Menactra vaccine participants achieved seroconversion rates of: 57%, Serogroup A (n=12/21); 62%, Serogroup C (n=29/47); 84%, serogroup Y (n=26/31); 53%, serogroup W-135 (n=20/38). The seroconversion rates for Menomune–A/C/Y/W-135 vaccine recipients were 55%, Serogroup A (n=16/29); 30%, Serogroup C (n=13/43); 57%, serogroup Y (n=17/30); 26%, serogroup W-135 (n=11/43).

In the subset of participants 4–10 years of age, percentages of participants that achieved seroconversion were similar between the Menactra vaccine and Menomune–A/C/Y/W-135 vaccine recipients. Menactra vaccine participants achieved seroconversion rates of: 69%, Serogroup A (n=11/16); 81%, Serogroup C (n=50/62); 98%, serogroup Y (n=45/46); 69%, serogroup W-135 (n=27/39). The seroconversion rates for Menomune–A/C/Y/W-135 vaccine recipients were 48%, Serogroup A (n=10/21); 38%, Serogroup C (n=19/50); 84%, serogroup Y (n=38/45); 68%, serogroup W-135 (n=26/38).

Immunogenicity in Adolescents

Results from the comparative clinical trial conducted in 881 adolescents aged 11–18 years showed that the immune responses to Menactra vaccine and Menomune–A/C/Y/W-135 vaccine were similar for all four serogroups (**Table 3**).

Table 3: Comparison of Bactericidal Antibody Responses* to Menactra Vaccine and Menomune–A/C/Y/W-135 Vaccine 28 Days after Vaccination for Participants Aged 11–18 Years

		Menactra vaccine N‡=423		Menomune–A/C/Y/W-135 vaccine N‡=423	
Serogroup			**(95% CI)§**		**(95% CI)§**
A	% ≥4-fold rise†	92.7	(89.8, 95.0)	92.4	(89.5, 94.8)
	GMT	5483	(4920, 6111)	3246	(2910, 3620)
C	% ≥4-fold rise†	91.7	(88.7, 94.2)	88.7	(85.2, 91.5)
	GMT	1924	(1662, 2228)	1639	(1406, 1911)
Y	% ≥4-fold rise†	81.8	(77.8, 85.4)	80.1	(76.0, 83.8)
	GMT	1322	(1162, 1505)	1228	(1088, 1386)
W-135	% ≥4-fold rise†	96.7	(94.5, 98.2)	95.3	(92.8, 97.1)
	GMT	1407	(1232, 1607)	1545	(1384, 1725)

* Serum Bactericidal Assay with baby rabbit complement (SBA-BR).

† Menactra vaccine was non-inferior to Menomune–A/C/Y/W-135 vaccine. Non-inferiority was assessed by the proportion of participants with a 4-fold or greater rise in SBA-BR titer for *N meningitidis* serogroups A, C, Y and W-135 using a 10% non-inferiority margin and a one-sided Type I error rate of 0.05.

‡ N = Number of participants with valid serology results at Day 0 and Day 28.

§ The 95% CI for the Geometric Mean Titer (GMT) was calculated based on an approximation to the normal distribution.

In participants with undetectable pre-vaccination titers (ie, less than 8 at Day 0), seroconversion rates (defined as a ≥4-fold rise in Day 28 SBA titers) were similar between the Menactra vaccine and Menomune–A/C/Y/W-135 vaccine recipients. Menactra vaccine participants achieved seroconversion rates of: 100%, Serogroup A (n=81/81); 99%, Serogroup C (n=153/155); 98%, Serogroup Y (n=60/61); 99%, Serogroup W-135 (n=161/164). The seroconversion rates for Menomune–A/C/Y/W-135 vaccine recipients were 100%, Serogroup A (n=93/93); 99%, Serogroup C (n=151/152); 100%, Serogroup Y (n=47/47); 99%, Serogroup W-135 (n=138/139).

Immunogenicity in Adults

Results from the comparative clinical trial conducted in 2554 adults aged 18–55 years showed that the immune responses to Menactra vaccine and Menomune–A/C/Y/W-135 vaccine were similar for all four serogroups (**Table 4**).

Table 4: Comparison of Bactericidal Antibody Responses* to Menactra Vaccine and Menomune–A/C/Y/W-135 Vaccine 28 Days After Vaccination for Participants Aged 18–55 Years

		Menactra vaccine N‡=1280		Menomune–A/C/Y/W-135 vaccine N‡=1098	
Serogroup			**(95% CI)§**		**(95% CI)§**
A	% ≥4-fold rise†	80.5	(78.2, 82.6)	84.6	(82.3, 86.7)
	GMT	3897	(3647, 4164)	4114	(3832, 4417)
C	% ≥4-fold rise†	88.5	(86.6, 90.2)	89.7	(87.8, 91.4)
	GMT	3231	(2955, 3533)	3469	(3148, 3823)
Y	% ≥4-fold rise†	73.5	(71.0, 75.9)	79.4	(76.9, 81.8)
	GMT	1750	(1597, 1918)	2449	(2237, 2680)
W-135	% ≥4-fold rise†	89.4	(87.6, 91.0)	94.4	(92.8, 95.6)
	GMT	1271	(1172, 1378)	1871	(1723, 2032)

* Serum Bactericidal Assay with baby rabbit complement (SBA-BR).

† Menactra vaccine was non-inferior to Menomune–A/C/Y/W-135 vaccine. Non-inferiority was assessed by the proportion of participants with a 4-fold or greater rise in SBA-BR titer for *N meningitidis* serogroups A, C, Y and W-135 using a 10% non-inferiority margin and a one-sided Type I error rate of 0.05.
‡ N = Number of participants with valid serology results at Day 0 and Day 28.
§ The 95% CI for the GMT was calculated based on an approximation to the normal distribution.

In participants with undetectable pre-vaccination titers (ie, less than 8 at Day 0), seroconversion rates (defined as a ≥4-fold rise in Day 28 SBA titers) were similar between the Menactra vaccine and Menomune–A/C/Y/W-135 vaccine recipients. Menactra vaccine participants achieved seroconversion rates of: 100%, Serogroup A (n=156/156); 99%, Serogroup C (n=343/345); 91%, Serogroup Y (n=253/279); 97%, Serogroup W-135 (n=360/373). The seroconversion rates for Menomune–A/C/Y/W-135 vaccine recipients were 99%, Serogroup A (n=143/144); 98%, Serogroup C (n=297/304); 97%, Serogroup Y (n=221/228); 99%, Serogroup W-135 (n=325/328).

Concomitant Vaccine Administration

Tetanus and Diphtheria

The concomitant use of Menactra vaccine and Tetanus and Diphtheria Toxoids Adsorbed, For Adult Use (Td, manufactured by Sanofi Pasteur Inc., Swiftwater, PA) was evaluated in a double-blind, randomized, controlled clinical trial conducted in 1021 participants aged 11–17 years. One group received Td and Menactra vaccines (at separate injection sites) at Day 0 and a saline placebo 28 days later (N=509). The other group received Td and a saline placebo at Day 0 and Menactra vaccine 28 days later (N=512). Sera were obtained approximately 28 days after each respective vaccination. As shown in **Table 5**, for meningococcal serogroups C, Y and W-135, the proportion of participants with a 4-fold or greater rise in SBA-BR titer was higher when Menactra vaccine was given concomitantly with Td than when Menactra vaccine was given one month following Td. The clinical relevance of this finding has not been fully evaluated. No interference was observed in the immune response to the tetanus and diphtheria components following concomitant vaccination (see **Table 5** and **DOSAGE AND ADMINISTRATION** section).[13]

Table 5: Comparison of Antibody Responses for Td* and Menactra† Vaccines for Participants Aged 11–17 Years on Day 28 Following Respective Vaccinations

		Td + Menactra vaccines at Day 0 Placebo at Day 28			Td + Placebo at Day 0 Menactra vaccine at Day 28		
Antigen		**N‡**		**(95% CI)§**	**N‡**		**(95% CI)§**
Tetanus	% >0.1 IU/mL‖	464	100	(99.2, 100.0)	477	100	(99.2, 100.0)
	GMT	464	11.5	(10.8, 12.2)	477	13.6	(12.7, 14.4)
Diphtheria	% >0.1 IU/mL¶	465	100	(99.2, 100.0)	473	100	(99.2, 100.0)
	GMT	465	120.9	(104.6, 139.8)	473	8.4	(7.6, 9.2)
Serogroup A	% ≥4-fold rise#	465	90.1	(87.4, 92.8)	478	90.6	(88.0, 93.2)
	GMT	466	11313	(10163, 12593)	478	10391	(9523, 11339)
Serogroup C	% ≥4-fold rise#	465	91.2	(88.6, 93.8)	478	82.4	(79.0, 85.8)
	GMT	466	5059	(4404, 5812)	478	2136	(1811, 2519)
Serogroup Y	% ≥4-fold rise#	465	85.8	(82.6, 89.0)	478	65.1	(60.8, 69.3)
	GMT	466	3391	(2981, 3858)	478	1331	(1170, 1515)
Serogroup W-135	% ≥4-fold rise#	465	96.3	(94.6, 98.1)	478	87.7	(84.7, 90.6)
	GMT	466	4195	(3719, 4731)	478	1339	(1162, 1543)

* Response to Td assessed as follows: Tetanus ELISA and Diphtheria MIT (Micrometabolic Inhibition Test) (IU/mL).
† Response to Menactra vaccine assessed by Serum Bactericidal Assay with baby rabbit complement (SBA-BR).
‡ N = Total number of participants with valid serology results on Day 28 (and on Day 0 for assessment of % ≥4-fold rise).
§ The 95% CI for the GMT is calculated based on an approximation to the normal distribution.
‖ A serum tetanus antitoxin level of at least 0.01 IU/mL, as measured by neutralization assay, is considered the minimum protective level.[14] A level ≥0.1 to 0.2 IU/mL has been considered as protective.[15]
¶ A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective.[14]
# Menactra vaccine when given concomitantly with Td was non-inferior to Menactra vaccine when given 28 days after Td. Non-inferiority was assessed by the proportion of participants with a 4-fold or greater rise in SBA-BR titer for *N meningitidis* serogroups A, C, Y and W-135 using a 10% non-inferiority margin and a one-sided Type I error rate of 0.05.

Typhoid Vi Polysaccharide Vaccine, Typhim Vi®

The concomitant use of Menactra vaccine and Typhim Vi vaccine (recommended for certain travelers) was evaluated in a double-blind, randomized, controlled clinical trial conducted in 945 participants aged 18–55 years. One group received Typhim Vi vaccine and Menactra vaccine (at separate injection sites) at Day 0 and a saline placebo 28 days later (N=469). The other group received Typhim Vi vaccine and a saline placebo at Day 0 and Menactra vaccine 28 days later (N=476). Sera were obtained approximately 28 days after each respective vaccination. The immune response to Menactra vaccine and to Typhim Vi vaccine when given concurrently was comparable to the immune response when Menactra vaccine or Typhim Vi vaccine was given alone (see **Table 6** and **DOSAGE AND ADMINISTRATION** section).[13]

Table 6: Comparison of Antibody Responses for Typhim Vi* and Menactra† Vaccines for Participants Aged 18–55 Years on Day 28 Following Respective Vaccinations

		Typhim Vi + Menactra vaccines at Day 0 Placebo at Day 28			Typhim Vi vaccine + Placebo at Day 0 Menactra vaccine at Day 28		
Antigen		**N‡**		**(95% CI)§**	**N‡†**		**(95% CI)§**
Typhoid Vi	GMT	418	2.4	(2.2, 2.7)	418	2.1	(1.9, 2.3)
Serogroup A	% ≥4-fold rise‖	418	79.7	(75.8, 83.5)	419	75.2	(71.0, 79.3)
	GMT	419	5138	(4490, 5879)	420	5110	(4523, 5772)
Serogroup C	% ≥4-fold rise‖	418	89.5	(86.5, 92.4)	419	88.3	(85.2, 91.4)
	GMT	419	3061	(2525, 3711)	420	3145	(2635, 3755)
Serogroup Y	% ≥4-fold rise‖	418	74.4	(70.2, 78.6)	419	65.2	(60.6, 69.7)
	GMT	419	1821	(1534, 2161)	420	1742	(1455, 2086)
Serogroup W-135	% ≥4-fold rise‖	418	85.2	(81.8, 88.6)	419	83.8	(80.2, 87.3)
	GMT	419	1002	(823, 1220)	420	929	(750, 1150)

* Response to Typhim Vi vaccine assessed by Anti Typhoid Vi RIA (Radioimmunoassay) (µg/mL).
† Response to Menactra vaccine assessed by Serum Bactericidal Assay with baby rabbit complement (SBA-BR).
‡ N = Number of participants with valid serology results at Day 28 (and Day 0 for assessment of % ≥4-fold rise).
§ The 95% CI for the GMT is calculated based on an approximation to the normal distribution.
‖ Menactra vaccine when given concomitantly with Typhim Vi vaccine was non-inferior to Menactra vaccine when given 28 days after Typhim Vi vaccine. Non-inferiority was assessed by the proportion of participants with a 4-fold or greater rise in SBA-BR titer for *N meningitidis* serogroups A, C, Y and W-135 using a 10% non-inferiority margin and a one-sided Type I error rate of 0.05.

INDICATIONS AND USAGE

Menactra vaccine is indicated for active immunization of individuals 2 through 55 years of age for the prevention of invasive meningococcal disease caused by *N meningitidis* serogroups A, C, Y and W-135.

Menactra vaccine is not indicated for the prevention of meningitis caused by other microorganisms or for the prevention of invasive meningococcal disease caused by *N meningitidis* serogroup B.

Menactra vaccine is not indicated for treatment of meningococcal infections.

Menactra vaccine is not indicated for immunization against diphtheria.

Menactra vaccine may not protect 100% of individuals.

CONTRAINDICATIONS

Known hypersensitivity to any component of Menactra vaccine including diphtheria toxoid, or a life-threatening reaction after previous administration of a vaccine containing similar components,[16] are contraindications to vaccine administration.

Known history of Guillain-Barré syndrome (see **WARNINGS** section) is a contraindication to vaccine administration.

Known hypersensitivity to dry natural rubber latex (see **WARNINGS** section) is a contraindication to vaccine administration.

WARNINGS

Guillain-Barré syndrome (GBS) has been reported in temporal relationship following administration of Menactra vaccine. An evaluation of post-marketing adverse events suggests a potential for an increased risk of GBS following Menactra vaccination[17] (see **ADVERSE REACTIONS, Post-Marketing Reports** section). Persons previously diagnosed with GBS should not receive Menactra vaccine.

The stopper of the vial contains dry natural rubber latex, which may cause allergic reactions in latex-sensitive individuals. There is no latex in any component of the syringe.

The ACIP has published guidelines for vaccination of persons with recent or acute illness (refer to www.cdc.gov).[15]

PRECAUTIONS

General

Before administration, all appropriate precautions should be taken to prevent adverse reactions. This includes a review of the patient's previous immunization history, the presence of any contraindications to immunization, the current health status, and history concerning possible sensitivity to the vaccine, similar vaccine, or to latex.

As a precautionary measure, epinephrine injection (1:1000) and other appropriate agents and equipment must be immediately available in case of anaphylactic or serious allergic reactions.

Special care should be taken to avoid injecting the vaccine subcutaneously since clinical studies have not been conducted to establish safety and efficacy of the vaccine using this route of administration.

The immune response to Menactra vaccine administered to immunosuppressed persons has not been studied.

Information for Patients

Prior to administration of Menactra vaccine, the health-care professional should inform the patient, parent, guardian, or other responsible adult of the potential benefits and risks to the patient (see **ADVERSE REACTIONS** and **WARNINGS** sections). The patient, parent or guardian should be given the Vaccine Information Statement, which is required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines). Patients, parents or guardians should be instructed to report any suspected adverse reactions to their health-care professional who should report these events to Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463.

Patients, parents or guardians should be informed that the US Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine and be given the contact information for VAERS (see **ADVERSE REACTIONS, Reporting of Adverse Events** section).

Females of childbearing potential should be informed that Sanofi Pasteur Inc. maintains a pregnancy registry to monitor fetal outcomes of pregnant women exposed to Menactra vaccine. If they are pregnant or become aware they were pregnant at the time of Menactra vaccine immunization, they should contact their healthcare professional or Sanofi Pasteur Inc. at 1-800-822-2463 (see **PRECAUTIONS** section).

Drug Interactions

For information regarding concomitant administration of Menactra vaccine with other vaccines, refer to **CLINICAL PHARMACOLOGY, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION** sections.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune response to vaccines.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Menactra vaccine has not been evaluated in animals for its carcinogenic or mutagenic potentials or for impairment of fertility.

Pregnancy Category C

Animal reproduction studies have not been conducted with Menactra vaccine. It is also not known whether Menactra vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. There are no adequate and well controlled studies in pregnant women. Menactra vaccine should only be given to a pregnant woman if clearly needed. Assessment of the effects on animal reproduction has not been fully conducted with Menactra vaccine as effects on male fertility in animals has not been evaluated. The effect of Menactra vaccine on embryo-fetal and pre-weaning development was evaluated in one developmental toxicity study in mice. Animals were administered Menactra vaccine on Day 14 prior to gestation and during the period of organogenesis (gestation Day 6). The total dose given per time point was 0.1 mL/mouse via intramuscular injection (900 times the human dose, adjusted by body weight). There were no adverse effects on pregnancy, parturition, lactation or pre-weaning development noted in this study. Skeletal examinations revealed one fetus (1 of 234 examined) in the vaccine group with a cleft palate. None were observed in the concurrent control group (0 of 174 examined). There are no data that suggest that this isolated finding is vaccine related, and there were no vaccine related fetal malformations or other evidence of teratogenesis observed in this study. Health care providers are encouraged to register pregnant women who receive Menactra vaccine in Sanofi Pasteur Inc.'s vaccination pregnancy registry by calling 1-800-822-2463.

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 Menactra vaccine is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Menactra vaccine in children below the age of 2 years have not been established.

Geriatric Use

Safety and effectiveness of Menactra vaccine in adults older than 55 years have not been established.

ADVERSE REACTIONS

The safety of Menactra vaccine was evaluated in 8 clinical studies that enrolled 10,057 participants aged 2–55 years who received Menactra vaccine and 5266 participants who received Menomune–A/C/Y/W-135 vaccine. There were no substantive differences in demographic characteristics between the vaccine groups. Among Menactra vaccine recipients of all ages, 24.0%, 16.2%, 40.4% and 19.4% were in the 2–10 year age range, 11–14, 15–25 and 26–55-year age groups, respectively. Among Menomune–A/C/Y/W-135 vaccine recipients of all ages, 42.3%, 9.3%, 30.0% and 18.5% were in the 2–10 year age range, 11–14, 15–25 and 26–55-year age groups, respectively.

The three primary safety studies were randomized, active-controlled trials that enrolled participants 2–10 years of age (Menactra vaccine, N=1713; Menomune–A/C/Y/W-135 vaccine, N=1519), 11–18 years of age (Menactra vaccine, N=2270; Menomune–A/C/Y/W-135 vaccine, N=972) and 18–55 years of age (Menactra vaccine, N=1384; Menomune–A/C/Y/W-135 vaccine, N=1170), respectively. Of the 3232 children 2–10 years old, 68% of participants (Menactra vaccine, n=1164; Menomune–A/C/Y/W-135 vaccine, n=1031) were enrolled at US sites, and 32% of participants at a Chilean site. The median ages in the Chilean and US subpopulations were 5 and 6 years old, respectively. All adolescents and adults were enrolled at US sites. As the route of administration differed for the two vaccines (Menactra vaccine given intramuscularly, Menomune–A/C/Y/W-135 vaccine given subcutaneously), study personnel collecting the safety data differed from personnel administering the vaccine. Solicited local and systemic reactions were monitored daily for 7 days post-vaccination using a diary card. Participants were monitored for 28 days for unsolicited adverse events and for 6 months post-vaccination for visits to an emergency room, unexpected visits to an office physician, and serious adverse events. Unsolicited adverse event information was obtained either by telephone interview or at an interim clinic visit. Information regarding adverse events that occurred in the 6-month post-vaccination time period was obtained via a scripted telephone interview. At least 94% of participants from the three primary studies completed the 6-month follow-up evaluation.

In the two concomitant vaccination studies with Menactra and either Typhim Vi or Td vaccines, local and systemic adverse events were monitored for 7 days post-vaccination using a diary card. Serious adverse events occurring within 1 month after each vaccination were reported and recorded.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the 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 adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

Serious Adverse Events in All Safety Studies

Serious adverse events reported within a 6-month time period following vaccination in children 2–10 years old occurred at a rate of 0.6% following Menactra vaccine and at a rate of 0.7% following Menomune–A/C/Y/W-135 vaccine. Serious adverse events reported within a 6-month time period following vaccination in adolescents and adults occurred at a rate of 1.0% following Menactra vaccine and at a rate of 1.3% following Menomune–A/C/Y/W-135 vaccine.

Solicited Adverse Events in the Primary Safety Studies

The most frequently reported solicited local and systemic adverse reactions in US children aged 2–10 years (**Table 7**) were injection site pain and irritability. Diarrhea, drowsiness, and anorexia were also common.

The most commonly reported solicited local and systemic adverse reactions in adolescents, ages 11–18 years (**Table 8**), and adults, ages 18–55 years (**Table 9**), were injection site pain, headache and fatigue. Except for redness in adults, local reactions were more frequently reported after Menactra vaccination than after Menomune–A/C/Y/W-135 vaccination. The majority of local and systemic reactions following Menactra or Menomune–A/C/Y/W-135 vaccination were reported as mild in intensity. Between the vaccine groups, differences in rates of malaise, diarrhea, anorexia, vomiting, or rash, including urticaria were not statistically significant.

Table 7: Percentage of US Participants 2–10 Years of Age Reporting Solicited Adverse Reactions Within 7 Days Following Vaccine Administration

	Menactra vaccine *N=1157			Menomune–A/C/Y/W-135 vaccine *N=1027		
Reaction	**Any**	**Moderate**	**Severe**	**Any**	**Moderate**	**Severe**
Redness†	21.8	4.6	3.9	7.9	0.5	0.0
Swelling†	17.4	3.9	1.9	2.8	0.3	0.0
Induration†	18.9	3.4	1.4	4.2	0.6	0.0
Pain‡	45.0	4.9	0.3	26.1	2.5	0.0
Drowsiness§	10.8	2.7	0.3	11.2	2.5	0.5
Irritability‖	12.4	3.0	0.3	12.2	2.6	0.6
Arthralgia¶	6.8	0.5	0.2	5.3	0.7	0.0
Diarrhea#	11.1	2.1	0.2	11.8	2.5	0.3
Anorexia**	8.2	1.7	0.4	8.7	1.3	0.8
Fever††	5.2	1.7	0.3	5.2	1.7	0.2
Vomiting‡‡	3.0	0.7	0.3	2.7	0.7	0.6
Rash§§	3.4			3.0		
Seizure§§	0.0			0.0		

* N = The total number of subjects reporting at least one solicited reaction. The median age of participants was 6 years in both vaccine groups.

† Moderate: 1.0-2.0 inches, Severe: >2.0 inches.

‡ Moderate: interferes with normal activities, Severe: disabling, unwilling to move arm.

§ Moderate: interferes with normal activities, Severe: disabling, unwilling to engage in play or interact with others.

‖ Moderate: 1-3 hours duration, Severe: >3 hours duration.

¶ Moderate: Decreased range of motion due to pain or discomfort, Severe: unable to move major joints due to pain.

\# Moderate: 3-4 episodes, Severe: ≥5 episodes.

** Moderate: Skipped 2 meals, Severe: skipped ≥3 meals.
†† Oral equivalent temperature; Moderate: 38.4-39.4ºC, Severe: ≥39.5ºC.
‡‡ Moderate: 2 episodes, Severe: ≥3 episodes.
§§ These solicited adverse events were reported as present or absent only.

Table 8: Percentage of Participants 11–18 Years of Age Reporting Solicited Adverse Reactions Within 7 Days Following Vaccine Administration

	Menactra vaccine N*=2264			Menomune–A/C/Y/W-135 vaccine N*=970		
Reaction	**Any**	**Moderate**	**Severe**	**Any**	**Moderate**	**Severe**
Redness‡	10.9†	1.6†	0.6†	5.7	0.4	0.0
Swelling‡	10.8†	1.9†	0.5†	3.6	0.3	0.0
Induration‡	15.7†	2.5†	0.3	5.2	0.5	0.0
Pain§	59.2†	12.8†	0.3	28.7	2.6	0.0
Headache||	35.6†	9.6†	1.1	29.3	6.5	0.4
Fatigue||	30.0†	7.5	1.1†	25.1	6.2	0.2
Malaise||	21.9†	5.8†	1.1	16.8	3.4	0.4
Arthralgia||	17.4†	3.6†	0.4	10.2	2.1	0.1
Diarrhea¶	12.0	1.6	0.3	10.2	1.3	0.0
Anorexia#	10.7†	2.0	0.3	7.7	1.1	0.2
Chills||	7.0†	1.7†	0.2	3.5	0.4	0.1
Fever**	5.1†	0.6	0.0	3.0	0.3	0.1
Vomiting††	1.9	0.4	0.3	1.4	0.5	0.3
Rash‡‡	1.6			1.4		
Seizure‡‡	0.0			0.0		

* N = The number of subjects with available data.
† Denotes ρ <0.05 level of significance. The *p* values were calculated for each category and severity using Chi Square test.
‡ Moderate: 1.0-2.0 inches, Severe: >2.0 inches.
§ Moderate: Interferes with or limits usual arm movement, Severe: Disabling, unable to move arm.
|| Moderate: Interferes with normal activities, Severe: Requiring bed rest.
¶ Moderate: 3-4 episodes, Severe: ≥5 episodes.
# Moderate: Skipped 2 meals, Severe: Skipped ≥3 meals.
** Oral equivalent temperature; Moderate: 38.5-39.4ºC, Severe: ≥39.5ºC.
†† Moderate: 2 episodes, Severe: ≥3 episodes.
‡‡ These solicited adverse events were reported as present or absent only.

Table 9: Percentage of Participants 18–55 Years of Age Reporting Solicited Adverse Reactions Within 7 Days Following Vaccine Administration

	Menactra vaccine N*=1371			Menomune–A/C/Y/W-135 vaccine N*=1159		
Reaction	**Any**	**Moderate**	**Severe**	**Any**	**Moderate**	**Severe**
Redness‡	14.4	2.9	1.1†	16.0	1.9	0.1
Swelling‡	12.6†	2.3†	0.9†	7.6	0.7	0.0
Induration‡	17.1†	3.4†	0.7†	11.0	1.0	0.0
Pain§	53.9†	11.3†	0.2	48.1	3.3	0.1
Headache||	41.4	10.1	1.2	41.8	8.9	0.9
Fatigue||	34.7	8.3	0.9	32.3	6.6	0.4
Malaise||	23.6	6.6†	1.1	22.3	4.7	0.9
Arthralgia||	19.8†	4.7†	0.3	16.0	2.6	0.1
Diarrhea¶	16.0	2.6	0.4	14.0	2.9	0.3
Anorexia#	11.8	2.3	0.4	9.9	1.6	0.4
Chills||	9.7†	2.1†	0.6†	5.6	1.0	0.0
Fever**	1.5†	0.3	0.0	0.5	0.1	0.0
Vomiting††	2.3	0.4	0.2	1.5	0.2	0.4
Rash‡‡	1.4			0.8		
Seizure‡‡	0.0			0.0		

* N = The number of subjects with available data.
† Denotes ρ <0.05 level of significance. The *p* values were calculated for each category and severity using Chi Square test.
‡ Moderate: 1.0-2.0 inches, Severe: >2.0 inches.
§ Moderate: Interferes with or limits usual arm movement, Severe: Disabling, unable to move arm.
|| Moderate: Interferes with normal activities, Severe: Requiring bed rest.
¶ Moderate: 3-4 episodes, Severe: ≥5 episodes.
# Moderate, Skipped 2 meals, Severe: Skipped ≥3 meals.
** Oral equivalent temperature; Moderate: 39.0-39.9ºC, Severe: ≥40.0ºC.
†† Moderate: 2 episodes, Severe: ≥3 episodes.
‡‡ These solicited adverse events were reported as present or absent only.

Adverse Events in Concomitant Vaccine Studies

Local and Systemic Reactions when Given with Td Vaccine

See **Concomitant Vaccine Administration** section for a description of the study design and number of participants. The two vaccine groups reported similar frequencies of pain, induration, redness and swelling at the Menactra injection site, as well as, at the Td injection site. Pain was the most frequent local reaction reported at both the Menactra and Td injection sites. More participants experienced pain after Td vaccination than after Menactra vaccination (71% versus 53%). The majority (66%-77%) of local solicited reactions for both groups at either injection site were reported as mild and resolved within 3 days post-vaccination.

The overall rate of systemic adverse events was higher when Menactra and Td vaccines were given concomitantly than when Menactra vaccine was administered 28 days after Td. In both groups, the most common reactions were headache (Menactra vaccine + Td, 36%; Td + Placebo, 34%; Menactra vaccine alone, 22%) and fatigue (Menactra vaccine + Td, 32%; Td + Placebo, 29%; Menactra vaccine alone, 17%). Between the groups, differences in rates of malaise, diarrhea, anorexia, vomiting, or rash were not statistically significant. Fever ≥40.0ºC occurred at ≤0.5% in all groups. No seizures occurred in either group.

Local and Systemic Reactions when Given with Typhim Vi Vaccine

See **Concomitant Vaccine Administration** section for a description of the study design and number of participants. The two vaccine groups reported similar frequencies of pain, induration, redness and swelling at the Menactra injection site, as well as, at the Typhim Vi injection site. Pain was the most frequent local reaction reported at both the Menactra and Typhim Vi injection sites. More participants experienced pain after Typhim Vi vaccination than after Menactra vaccination (76% versus 47%). The majority (70%-77%) of local solicited reactions for both groups at either injection site were reported as mild and resolved within 3 days post-vaccination. In both groups, the most common systemic reaction was headache (Menactra + Typhim Vi vaccine, 41%; Typhim Vi vaccine + Placebo, 42%; Menactra vaccine alone, 33%) and fatigue (Menactra + Typhim Vi vaccine, 38%; Typhim Vi vaccine + Placebo, 35%; Menactra vaccine alone, 27%). Between the groups, differences in rates of malaise, diarrhea, anorexia, or vomiting were not statistically significant. Fever ≥40.0ºC and seizures were not reported in either group.

Post-Marketing Reports

The following adverse events have been reported during post-approval use of Menactra vaccine. Because these events were reported voluntarily from a population of uncertain size, it is not always possible to reliably calculate their frequency or to establish a causal relationship to Menactra vaccine exposure.

Nervous system disorders - Guillain-Barré syndrome, vasovagal syncope, facial palsy, transverse myelitis, acute disseminated encephalomyelitis
Skin and subcutaneous tissue disorders - Urticaria
Musculoskeletal and connective tissue disorders - Myalgia

Reporting of Adverse Events

Vaccine Adverse Event Reporting System (VAERS) was established by the US Department of Health and Human Services to accept all reports of suspected adverse events after the administration of any vaccine. Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967 or through http://vaers.hhs.gov.[18] Reporting to VAERS of all adverse events after vaccination by parents, guardians or adult patients should be encouraged.

Health-care providers should also report these events to Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION

Menactra vaccine should be administered as a single 0.5 mL injection by the **intramuscular** route, preferably in the deltoid region.

Do not administer this product intravenously, subcutaneously, or intradermally.

The need for, or timing of, a booster dose of Menactra vaccine has not yet been determined.

Parenteral drug products should be inspected visually for container integrity, particulate matter and discoloration prior to administration, whenever solution and container permit.

Concomitant Administration with Other Vaccines

Safety and immunogenicity data are available on concomitant administration of Menactra vaccine with Typhim Vi, and Td vaccines (see **CLINICAL PHARMACOLOGY** and **ADVERSE REACTIONS** sections). Concomitant administration of Menactra vaccine with Td did not result in reduced tetanus, diphtheria or meningococcal antibody responses (see **Table 5**) compared with Menactra vaccine administered 28 days after Td.[13] However, for meningococcal serogroups C, Y and W-135, bactericidal antibody titers (GMTs) and the proportion of participants with a 4-fold or greater rise in SBA-BR titer were higher when Menactra vaccine was given concomitantly with Td than when Menactra vaccine was given one month following Td. The clinical relevance of these findings has not been fully evaluated.[13]

Concomitant administration of Menactra vaccine with Typhim Vi vaccine did not result in reduced antibody responses to any of the vaccine antigens (see **Table 6**).[13]

The safety and immunogenicity of concomitant administration of Menactra vaccine with vaccines other than Typhim Vi or Td vaccines have not been determined.

Menactra vaccine must not be mixed with any vaccine in the same syringe. Therefore, separate injection sites and different syringes should be used in case of concomitant administration (see **CLINICAL PHARMACOLOGY** section).

HOW SUPPLIED

BD Luer-Lok® latex-free syringe, 0.5 mL. Product No. 49281-589-11
BD Luer-Lok® latex-free syringe, 0.5 mL (5 x 0.5 mL syringes per package). Product No. 49281-589-15
Vial, 1 Dose (5 per package). Product No. 49281-589-05

Luer-Lok is a registered trademark of Becton Dickinson and Company.

STORAGE

Store at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product that has been exposed to freezing should not be used. Do not use after expiration date.

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Product Information
as of October 2007

Manufactured by:
Sanofi Pasteur Inc.
Swiftwater PA 18370 USA

sanofi pasteur