AHFS Category: 80:12

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

Menactra™

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 mg each of meningococcal A, C, Y, and W-135 polysaccharides conjugated to approximately 48 mg 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%.[6-9] 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.

In the United States (US), overall rates of meningococcal disease during the period 1967–2002 have remained stable, with yearly case counts varying from 1323–3525, reflecting a cyclical pattern with peaks occurring every 10–15 years.[10,11] The age-specific incidence of meningococcal disease continues to be highest among infants younger than one year old, among whom serogroup B predominates. The rate of meningococcal disease also peaks during adolescence and early adulthood.[12]

From 1989 to 2002, the proportion of all meningococcal cases due to serogroup Y increased from 2% to 29%, while serogroups B and C decreased from 46% and 45% of cases, to 24% and 34%, respectively. The remaining cases were caused by serogroup W-135 and other strains. In 2002, serogroups C and Y accounted for 42% and 24% of meningococcal cases, respectively, in adolescents and adults 18–49 years of age.[12–15]

Globally, serogroup A is the most common cause of epidemics in Africa and Asia, but a rare cause of disease in the US.[6] Outbreaks of serogroup W-135 have been reported among pilgrims returning from the Hajj to Saudi Arabia in 2000 and 2001.[16,17]

MECHANISM OF ACTION

The presence of bactericidal anti-capsular meningococcal antibodies has been associated with protection from invasive meningococcal disease.[18,19] 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. The primary measure of immune response was induction of serogroup-specific anti-capsular antibody that possessed bactericidal activity. The antibody response to vaccination was evaluated by determining the proportion of participants with a 4-fold or greater increase in serum bactericidal antibody to each serogroup. Sera from clinical trial participants were tested for these antibodies with a Serum Bactericidal Assay (SBA) using baby rabbit complement (SBA-BR).[20]

Immunogenicity was evaluated in two comparative, randomized, multi-center, active controlled clinical trials that enrolled male and female adolescents (11–18 years old) and adults (18–55 years old), respectively. Participants received a dose of Menactra vaccine (N=1824) or Menomune–A/C/Y/W-135 vaccine (N=1611). In each of the trials, there were no substantive differences in demographic characteristics between the vaccine groups. 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. (Blinding procedures for safety assessments are described in **ADVERSE REACTIONS** section.) Sera were obtained before and approximately 28 days after vaccination.

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 1).

TABLE 1: 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 (Primary Endpoint).

‡ 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 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 2).

TABLE 2: 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 (Primary Endpoint).

‡ 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 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 Aventis 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 3, 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 either concomitant or sequential vaccination (see TABLE 3 and **DOSAGE AND ADMINISTRATION** section).[21]

TABLE 3: 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 is considered the minimum protective level.[22]

¶ 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.[22]

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 responses to Menactra vaccine and to Typhim Vi vaccine when given concurrently were comparable to the immune response when Menactra vaccine or Typhim Vi vaccine was given alone (see TABLE 4 and **DOSAGE AND ADMINISTRATION** section).[21]

TABLE 4: 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 adolescents and adults 11–55 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.

The Advisory Committee on Immunization Practices (ACIP) has published recommendations for the prevention and control of meningococcal disease in the US (refer to www.cdc.gov).[5]

As with any vaccine, 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,[23] are contraindications to vaccine administration.

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

WARNINGS
The stopper of the vial contains dry natural rubber latex, which may cause allergic reactions in latex-sensitive individuals.

Because of the risk of hemorrhage, Menactra vaccine should not be given to persons with any bleeding disorder, such as hemophilia or thrombocytopenia, or to persons on anticoagulant therapy unless the potential benefit clearly outweighs the risk of administration. If the decision is made to administer Menactra vaccine in such persons, it should be given with caution, with steps taken to avoid the risk of bleeding or hematoma formation following injection.

The ACIP has published guidelines for vaccination of persons with recent or acute illness (refer to www.cdc.gov).[24]

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.

As part of the patient's immunization record, the date, lot number and manufacturer of the vaccine administered should be recorded.

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.

A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of blood borne infectious agents from person to person. Needles should not be recapped and should be disposed of according to biohazardous waste guidelines.

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

INFORMATION FOR PATIENTS

Prior to administration of Menactra vaccine, the healthcare professional should inform the patient, parent, guardian, or other responsible adult of the potential benefits and risks to the patient, and provide vaccine information statements (see **ADVERSE REACTIONS** and **WARNINGS** sections). Patients, parents or guardians should be instructed to report any suspected adverse reactions to their healthcare professional. Females of childbearing potential should be informed that Aventis 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 Aventis Pasteur Inc. at 1-800-822-2463 (see **PRECAUTIONS** section).

DRUG INTERACTION

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 were performed in mice using 0.2 mL of Menactra vaccine (900 times the human dose, adjusted by body weight). There were no effects on fertility, maternal health, embryo/fetal survival, or post-natal development. 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 no other skeletal and organ malformations were observed in this study. There are no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, Menactra vaccine should be used during pregnancy only if clearly needed. Health care providers are encouraged to register pregnant women who receive Menactra vaccine in Aventis 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 11 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 6 clinical studies that enrolled 7642 participants aged 11–55 years who received Menactra vaccine and 3041 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, 21.3%, 53.2% and 25.5% were in the 11–14, 15–25 and 26–55-year age groups, respectively. Among Menomune–A/C/Y/W-135 vaccine recipients of all ages, 16.1%, 51.9% and 32.0% were in the 11–14, 15–25 and 26–55-year age groups, respectively.

The two primary safety studies were randomized, active-controlled trials that enrolled participants 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. As the route of administration differed for the two vaccines (Menactra vaccine given intramuscularly, Menomune–A/C/Y/W-135 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 two 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 occurred at the same rate (1.3%) in the Menactra vaccine and Menomune–A/C/Y/W-135 vaccine groups. The events reported were consistent with events expected in healthy adolescent and adult populations.

SOLICITED ADVERSE EVENTS IN THE PRIMARY SAFETY STUDIES
The most commonly reported solicited adverse reactions in adolescents, ages 11–18 years (TABLE 5), and adults, ages 18–55 years (TABLE 6), were local 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. No important differences in rates of malaise, diarrhea, anorexia, vomiting, or rash were observed between the vaccine groups.

TABLE 5: PERCENTAGE OF PARTICIPANTS 11–18 YEARS OF AGE REPORTING SOLICITED REACTIONS

	Menactra vaccine			Menomune–A/C/Y/W-135 vaccine		
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		

* Denotes $\rho < 0.05$ 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 normal activities, Severe: Disabling, unwilling to move arm.
§ Severe: Requiring bed rest.
‖ Severe: ≥ 5 episodes.
¶ Severe: skipped ≥ 3 meals.
# Severe: ≥ 39.5ºC.
** Severe: ≥ 3 episodes.
†† These solicited adverse events were reported as present or absent only.

TABLE 6: PERCENTAGE OF PARTICIPANTS 18–55 YEARS OF AGE REPORTING SOLICITED REACTIONS

	Menactra vaccine			Menomune–A/C/Y/W-135 vaccine		
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		

* Denotes $\rho < 0.05$ 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 normal activities, Severe: Disabling, unwilling to move arm.
§ Severe: Requiring bed rest.
‖ Severe: ≥ 5 episodes.
¶ Severe: skipped ≥ 3 meals.
# Severe: ≥ 40.0ºC.
** 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 local 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%). No important differences in rates of malaise, diarrhea, anorexia, vomiting, or rash were observed between the groups. 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 local 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%). No important differences in rates of malaise, diarrhea, anorexia, vomiting, or rash were observed between the groups. Fever ≥ 40.0ºC and seizures were not reported in either group.

REPORTING OF ADVERSE EVENTS
The US Department of Health and Human Services has established the Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. Reporting of all adverse events occurring after vaccine administration is encouraged from vaccine recipients, parents/guardians and the health-care provider. Adverse events following immunization should be reported to VAERS. 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.[25] Reporting forms may also be obtained at the FDA web site at www.vaers.org.

Health-care providers should also report these events to the Pharmacovigilance Department, Aventis 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. Before injection, the skin at the injection site should be cleaned and prepared with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

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 3) compared with Menactra vaccine administered 28 days after Td.[21] 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.[21]

Concomitant administration of Menactra vaccine with Typhim Vi vaccine did not result in reduced antibody responses to any of the vaccine antigens (see TABLE 4).[21]

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

Vial, 1 Dose (1 per package). Product No. 49281-589-01
Vial, 1 Dose (5 per package). Product No. 49281-589-05
CPT® Code: 90734
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STORAGE

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

REFERENCES

1. Mueller JH, et al. A Protein-Free Medium for Primary Isolation of the Gonococcus and Meningococcus. Proc Soc Exp Biol Med 1941;48:330-333.
2. Watson RG, et al. The specific hapten of group C (group IIα) meningococcus. I. Preparation and immunological behavior. J Immunol 1958;81:331-336.
3. Mueller JH, et al. Production of diphtheria toxin of high potency (100 Lf) on a reproducible medium. J Immunol 1941;40:21-32.
4. Granoff DM, et al. Meningococcal Vaccines. Plotkin SA, Orenstein WA, eds. Vaccines 4th ed. Philadelphia: WB Saunders Co 2004:960.
5. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Prevention and Control of Meningococcal Disease and Meningococcal Disease and College Students. MMWR 2000;49;(RR-7).

6. Rosenstein NE, et al. Meningococcal Disease. N Engl J Med 2001;344:1378-1388.
7. World Health Organization (WHO). Group A and C meningococcal vaccines. Wkly Epidemiol Rec 1999;74:297-303.
8. Brassier N, et al. Meningococcal meningitis and meningococcemia: epidemiological study, France (1985-1991). Med Maklad Infect 1995;25:584-593.
9. Sorensen HT, et al. Outcome of Pre-hospital Antibiotic Treatment of Meningococcal Disease. J Clin Epidemiol 1998;51:717-721.
10. CDC. Summary of Notifiable Diseases, United States, 1996. MMWR 1997;45:1-14.
11. CDC. Summary of Notifiable Diseases, United States, 2002. MMWR 2004;51:1-34.
12. Rosenstein NE, et al. The Changing Epidemiology of Meningococcal Disease in the United States, 1992-1996. J Inf Dis 1999;180:1894-1901.
13. CDC. Laboratory-Based Surveillance for Meningococcal Disease in Selected Areas, United States, 1989-1991. MMWR 1993;42 (SS-2):21-40.
14. Harrison LH, et al. Invasive Meningococcal Disease in Adolescents and Young Adults. JAMA 2001;286:694-699.
15. CDC. Active Bacterial Core Surveillance (ABCs) Report, Emerging Infections Program Network, *Neisseria Meningitidis* Available at: http://www.cdc.gov/ncidod/dbmd/abcs/survreports.htm.
16. WHO. International Coordinating Group (ICG) on Vaccine Provision for Epidemic Meningitis Control. Report of the Seventh Meeting. 2001:3-5.
17. Decosas J, et al. Chronicle of an Outbreak Foretold: Meningococcal Meningitis W135 in Burkina Faso. Lancet 2002;2:763-765.
18. Mäkelä PH, et al. Evolution of conjugate vaccines. Expert Rev Vaccines 2002;1(3):399-410.
19. Goldschneider I, et al. Human immunity to the meningococcus. I. The Role of Humoral Antibodies. J Exp Med 1969;129:1307-1326.
20. Maslanka SE, et al. Standardization and a Multilaboratory Comparison of *Neisseria meningitidis* Serogroup A and C Serum Bactericidal Assays. Clin and Diag Lab Immunol 1997;156-167.
21. Data on file, Aventis Pasteur Inc. – 092503.
22. Department of Health and Human Services (DHHS), Food and Drug Administration (FDA). Biological Products; Bacterial vaccine and toxoids; Implementaion of efficacy rule; Proposed Rule. Federal Register December 13, 1985;50(240);51002-51117.
23. Ball R, et al. Safety Data on Meningococcal Polysaccharide Vaccine from the Vaccine Adverse Event Reporting System. CID 2001;32:1273-1280.
24. ACIP. General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). MMWR 2002;51(RR02):1-36.
25. CDC. Vaccine Adverse Event Reporting System – United States. MMWR 1990;39:730-733.

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Product information
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