

1 AHFS Category: 80:12

MCV4

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

R_x only



Menactra®

FOR INTRAMUSCULAR INJECTION

2

3 **DESCRIPTION**

4 Menactra®, Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid
5 Conjugate Vaccine, is a sterile, intramuscularly administered vaccine that contains *Neisseria*
6 *meningitidis* serogroup A, C, Y and W-135 capsular polysaccharide antigens individually
7 conjugated to diphtheria toxoid protein. *N meningitidis* A, C, Y and W-135 strains are cultured
8 on Mueller Hinton agar (1) and grown in Watson Scherp(2) media. The polysaccharides are
9 extracted from the *N meningitidis* cells and purified by centrifugation, detergent precipitation,
10 alcohol precipitation, solvent extraction and diafiltration. To prepare the polysaccharides for
11 conjugation, they are depolymerized, derivatized, and purified by diafiltration. *Corynebacterium*
12 *diphtheriae* cultures are grown in a modified Mueller and Miller medium (3) and detoxified with
13 formaldehyde. The diphtheria toxoid protein is purified by ammonium sulfate fractionation and
14 diafiltration. The derivatized polysaccharides are covalently linked to diphtheria toxoid and
15 purified by serial diafiltration. The four meningococcal components, present as individual

1 serogroup-specific glycoconjugates, compose the final formulated vaccine. No preservative or
2 adjuvant is added during manufacture. Potency of Menactra vaccine is determined by
3 quantifying the amount of each polysaccharide antigen that is conjugated to diphtheria toxoid
4 protein and the amount of unconjugated polysaccharide present.

5
6 Menactra vaccine is manufactured as a sterile, clear to slightly turbid liquid. Each 0.5 mL dose
7 of vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution to
8 contain 4 µg each of meningococcal A, C, Y, and W-135 polysaccharides conjugated to
9 approximately 48 µg of diphtheria toxoid protein carrier.

10

11 **CLINICAL PHARMACOLOGY**

12 **Background**

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

1 (5) of meningococcal disease survivors have sequelae such as hearing loss and neurologic
2 disability, or loss of skin, digits or limbs as a result of ischemia.

3

4 **Mechanism of Action**

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

9

10 **Clinical Studies**

11 Vaccine efficacy was inferred from the demonstration of immunologic equivalence to a US-
12 licensed meningococcal polysaccharide vaccine, Menomune®–A/C/Y/W-135, Meningococcal
13 Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined as assessed by Serum
14 Bactericidal Assay (SBA). The SBA used to test sera contained an exogenous complement
15 source that was either human (SBA-H) or, when correlated to SBA-H, baby rabbit (SBA-BR).
16 (12)

17

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

22

1 Immunogenicity was evaluated in three comparative, randomized, US, multi-center, active
2 controlled clinical trials that enrolled children (2–10 years old), adolescents (11–18 years old),
3 and adults (18–55 years old). Participants received a dose of Menactra vaccine (N=2526) or
4 Menomune–A/C/Y/W-135 vaccine (N=2317). For all age groups studied, sera were obtained
5 before and approximately 28 days after vaccination. (Blinding procedures for safety assessments
6 are described in **ADVERSE REACTIONS** section.)
7

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

15 **Immunogenicity in Children**

16 Of 1408 enrolled children 2–10 years old, immune responses evaluated in a subset of Menactra
17 vaccine participants (2–3 years old, n=52; 4–10 years old, n=84) and Menomune–A/C/Y/W-135
18 vaccine participants (2–3 years old, n=53; 4–10 years old, n=84) were comparable for all four
19 serogroups (**Table 1** and **Table 2**).
20

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

4 * Serum Bactericidal Assay with an exogenous human complement (SBA-H) source.

5 † The proportion of participants achieving at least an SBA-H titer of 1:8 was assessed using a 10% non-
 6 inferiority margin and a one-sided Type I error rate of 0.025.

7 ‡ N = Number of subset participants with at least one valid serology result at Day 0 and Day 28.

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

10

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

4 * Serum Bactericidal Assay with an exogenous human complement (SBA-H) source.

5 † The proportion of participants achieving at least an SBA-H titer of 1:8 was assessed using a 10% non-
 6 inferiority margin and a one-sided Type I error rate of 0.025.

7 ‡ N = Number of subset participants with at least one valid serology result at Day 0 and Day 28.

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

10

1 In the subset of participants 2–3 years of age with undetectable pre-vaccination titers (ie, <4 at
2 Day 0), seroconversion rates (defined as ≥ 8 at Day 28) were similar between the Menactra
3 vaccine and Menomune–A/C/Y/W-135 vaccine recipients. Menactra vaccine participants
4 achieved seroconversion rates of: 57%, Serogroup A (n=12/21); 62%, Serogroup C (n=29/47);
5 84%, serogroup Y (n=26/31); 53%, serogroup W-135 (n=20/38). The seroconversion rates for
6 Menomune–A/C/Y/W-135 vaccine recipients were 55%, Serogroup A (n=16/29); 30%,
7 Serogroup C (n=13/43); 57%, serogroup Y (n=17/30); 26%, serogroup W-135 (n=11/43).

8
9 In the subset of participants 4–10 years of age, percentages of participants that achieved
10 seroconversion were similar between the Menactra vaccine and Menomune–A/C/Y/W-135
11 vaccine recipients. Menactra vaccine participants achieved seroconversion rates of: 69%,
12 Serogroup A (n=11/16); 81%, Serogroup C (n=50/62); 98%, serogroup Y (n=45/46); 69%,
13 serogroup W-135 (n=27/39). The seroconversion rates for Menomune–A/C/Y/W-135 vaccine
14 recipients were 48%, Serogroup A (n=10/21); 38%, Serogroup C (n=19/50); 84%, serogroup Y
15 (n=38/45); 68%, serogroup W-135 (n=26/38).

16

17 **Immunogenicity in Adolescents**

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

21

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

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

5 † Menactra vaccine was non-inferior to Menomune–A/C/Y/W-135 vaccine. Non-inferiority was assessed
 6 by the proportion of participants with a 4-fold or greater rise in SBA-BR titer for *N meningitidis*
 7 serogroups A, C, Y and W-135 using a 10% non-inferiority margin and a one-sided Type I error rate of
 8 0.05.

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

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

3
4 In participants with undetectable pre-vaccination titers (ie, less than 8 at Day 0), seroconversion
5 rates (defined as a ≥ 4 -fold rise in Day 28 SBA titers) were similar between the Menactra vaccine
6 and Menomune–A/C/Y/W-135 vaccine recipients. Menactra vaccine participants achieved
7 seroconversion rates of: 100%, Serogroup A (n=81/81); 99%, Serogroup C (n=153/155); 98%,
8 Serogroup Y (n=60/61); 99%, Serogroup W-135 (n=161/164). The seroconversion rates for
9 Menomune–A/C/Y/W-135 vaccine recipients were 100%, Serogroup A (n=93/93); 99%,
10 Serogroup C (n=151/152); 100%, Serogroup Y (n=47/47); 99%, Serogroup W-135 (n=138/139).

11

12 **Immunogenicity in Adults**

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

16

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

		Menactra vaccine		Menomune–A/C/Y/W-135 vaccine	
		N [‡] =1280		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)

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

5 † Menactra vaccine was non-inferior to Menomune–A/C/Y/W-135 vaccine. Non-inferiority was assessed
 6 by the proportion of participants with a 4-fold or greater rise in SBA-BR titer for *N meningitidis*
 7 serogroups A, C, Y and W-135 using a 10% non-inferiority margin and a one-sided Type I error rate of
 8 0.05.

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

10 § The 95% CI for the GMT was calculated based on an approximation to the normal distribution.

1
2 In participants with undetectable pre-vaccination titers (ie, less than 8 at Day 0), seroconversion
3 rates (defined as a ≥ 4 -fold rise in Day 28 SBA titers) were similar between the Menactra vaccine
4 and Menomune–A/C/Y/W-135 vaccine recipients. Menactra vaccine participants achieved
5 seroconversion rates of: 100%, Serogroup A (n=156/156); 99%, Serogroup C (n=343/345); 91%,
6 Serogroup Y (n=253/279); 97%, Serogroup W-135 (n=360/373). The seroconversion rates for
7 Menomune–A/C/Y/W-135 vaccine recipients were 99%, Serogroup A (n=143/144); 98%,
8 Serogroup C (n=297/304); 97%, Serogroup Y (n=221/228); 99%, Serogroup W-135
9 (n=325/328).

10

11 **Concomitant Vaccine Administration**

12 Tetanus and Diphtheria

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

1 following concomitant vaccination (see [Table 5](#) and [DOSAGE AND ADMINISTRATION](#)
 2 section). (13)

3

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

		Td + Menactra vaccines			Td + Placebo		
		at Day 0			at Day 0		
		Placebo at Day 28			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)

-
- 1 * Response to Td assessed as follows: Tetanus ELISA and Diphtheria MIT (Micrometabolic Inhibition
2 Test) (IU/mL).
- 3 † Response to Menactra vaccine assessed by Serum Bactericidal Assay with baby rabbit complement
4 (SBA-BR).
- 5 ‡ N = Total number of participants with valid serology results on Day 28 (and on Day 0 for assessment of
6 % \geq 4-fold rise).
- 7 § The 95% CI for the GMT is calculated based on an approximation to the normal distribution.
- 8 || A serum tetanus antitoxin level of at least 0.01 IU/mL, as measured by neutralization assay, is considered
9 the minimum protective level. (14) A level \geq 0.1 to 0.2 IU/mL has been considered as protective. (15)
- 10 ¶ A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection.
11 Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. (14)
- 12 # Menactra vaccine when given concomitantly with Td was non-inferior to Menactra vaccine when given
13 28 days after Td. Non-inferiority was assessed by the proportion of participants with a 4-fold or greater
14 rise in SBA-BR titer for *N meningitidis* serogroups A, C, Y and W-135 using a 10% non-inferiority
15 margin and a one-sided Type I error rate of 0.05.
- 16

17 Typhoid Vi Polysaccharide Vaccine, Typhim Vi®

18 The concomitant use of Menactra vaccine and Typhim Vi vaccine (recommended for certain
19 travelers) was evaluated in a double-blind, randomized, controlled clinical trial conducted in 945
20 participants aged 18–55 years. One group received Typhim Vi vaccine and Menactra vaccine (at
21 separate injection sites) at Day 0 and a saline placebo 28 days later (N=469). The other group
22 received Typhim Vi vaccine and a saline placebo at Day 0 and Menactra vaccine 28 days later
23 (N=476). Sera were obtained approximately 28 days after each respective vaccination. The
24 immune response to Menactra vaccine and to Typhim Vi vaccine when given concurrently was

1 comparable to the immune response when Menactra vaccine or Typhim Vi vaccine was given
 2 alone (see [Table 6](#) and [DOSAGE AND ADMINISTRATION](#) section). (13)

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

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

5 * Response to Typhim Vi vaccine assessed by Anti Typhoid Vi RIA (Radioimmunoassay) (µg/mL).

6 † Response to Menactra vaccine assessed by Serum Bactericidal Assay with baby rabbit complement
 7 (SBA-BR).

1 ‡ N = Number of participants with valid serology results at Day 28 (and Day 0 for assessment of % \geq 4-fold
2 rise).

3 § The 95% CI for the GMT is calculated based on an approximation to the normal distribution.

4 || Menactra vaccine when given concomitantly with Typhim Vi vaccine was non-inferior to Menactra
5 vaccine when given 28 days after Typhim Vi vaccine. Non-inferiority was assessed by the proportion of
6 participants with a 4-fold or greater rise in SBA-BR titer for *N meningitidis* serogroups A, C, Y and W-
7 135 using a 10% non-inferiority margin and a one-sided Type I error rate of 0.05.
8

9 **INDICATIONS AND USAGE**

10 Menactra vaccine is indicated for active immunization of individuals 2 through 55 years of age
11 for the prevention of invasive meningococcal disease caused by *N meningitidis* serogroups A, C,
12 Y and W-135.
13

14 Menactra vaccine is not indicated for the prevention of meningitis caused by other
15 microorganisms or for the prevention of invasive meningococcal disease caused by *N*
16 *meningitidis* serogroup B.
17

18 Menactra vaccine is not indicated for treatment of meningococcal infections.
19

20 Menactra vaccine is not indicated for immunization against diphtheria.
21

22 Menactra vaccine may not protect 100% of individuals.
23

1 **CONTRAINDICATIONS**

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

5

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

8

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

11

12 **WARNINGS**

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

18

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

21

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

3

4 **PRECAUTIONS**

5 **General**

6 Before administration, all appropriate precautions should be taken to prevent adverse reactions.

7 This includes a review of the patient's previous immunization history, the presence of any
8 contraindications to immunization, the current health status, and history concerning possible
9 sensitivity to the vaccine, similar vaccine, or to latex.

10

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

13

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

17

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

20

21 **Information for Patients**

22 Prior to administration of Menactra vaccine, the health-care professional should inform the
23 patient, parent, guardian, or other responsible adult of the potential benefits and risks to the

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

8
9 Patients, parents or guardians should be informed that the US Department of Health and Human
10 Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all
11 reports of suspected adverse events after the administration of any vaccine and be given the
12 contact information for VAERS (see **ADVERSE REACTIONS, Reporting of Adverse Events**
13 section).

14
15 Females of childbearing potential should be informed that Sanofi Pasteur Inc. maintains a
16 pregnancy registry to monitor fetal outcomes of pregnant women exposed to Menactra vaccine.
17 If they are pregnant or become aware they were pregnant at the time of Menactra vaccine
18 immunization, they should contact their healthcare professional or Sanofi Pasteur Inc. at 1-800-
19 822-2463 (see **PRECAUTIONS** section).

20
21
22

1 **Drug Interactions**

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

5
6 Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic
7 drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune
8 response to vaccines.

9

10 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

13

14 **Pregnancy Category C**

15 Animal reproduction studies have not been conducted with Menactra vaccine. It is also not
16 known whether Menactra vaccine can cause fetal harm when administered to a pregnant woman
17 or can affect reproduction capacity. There are no adequate and well controlled studies in
18 pregnant women. Menactra vaccine should only be given to a pregnant woman if clearly needed.
19 Assessment of the effects on animal reproduction has not been fully conducted with Menactra
20 vaccine as effects on male fertility in animals has not been evaluated. The effect of Menactra
21 vaccine on embryo-fetal and pre-weaning development was evaluated in one developmental
22 toxicity study in mice. Animals were administered Menactra vaccine on Day 14 prior to
23 gestation and during the period of organogenesis (gestation Day 6). The total dose given per time

1 point was 0.1 mL/mouse via intramuscular injection (900 times the human dose, adjusted by
2 body weight). There were no adverse effects on pregnancy, parturition, lactation or pre-weaning
3 development noted in this study. Skeletal examinations revealed one fetus (1 of 234 examined)
4 in the vaccine group with a cleft palate. None were observed in the concurrent control group (0
5 of 174 examined). There are no data that suggest that this isolated finding is vaccine related, and
6 there were no vaccine related fetal malformations or other evidence of teratogenesis observed in
7 this study. Health care providers are encouraged to register pregnant women who receive
8 Menactra vaccine in Sanofi Pasteur Inc.'s vaccination pregnancy registry by calling 1-800-822-
9 2463.

10

11 **Nursing Mothers**

12 It is not known whether this drug is excreted in human milk. Because many drugs are excreted in
13 human milk, caution should be exercised when Menactra vaccine is administered to a nursing
14 woman.

15

16 **Pediatric Use**

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

19

20 **Geriatric Use**

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

23

1 **ADVERSE REACTIONS**

2 The safety of Menactra vaccine was evaluated in 8 clinical studies that enrolled 10,057
3 participants aged 2–55 years who received Menactra vaccine and 5266 participants who received
4 Menomune–A/C/Y/W-135 vaccine. There were no substantive differences in demographic
5 characteristics between the vaccine groups. Among Menactra vaccine recipients of all ages,
6 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
7 age groups, respectively. Among Menomune–A/C/Y/W-135 vaccine recipients of all ages,
8 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
9 age groups, respectively.

10

11 The three primary safety studies were randomized, active-controlled trials that enrolled
12 participants 2–10 years of age (Menactra vaccine, N=1713; Menomune–A/C/Y/W-135 vaccine,
13 N=1519), 11–18 years of age (Menactra vaccine, N=2270; Menomune–A/C/Y/W-135 vaccine,
14 N=972) and 18–55 years of age (Menactra vaccine, N=1384; Menomune–A/C/Y/W-135 vaccine,
15 N=1170), respectively. Of the 3232 children 2–10 years old, 68% of participants (Menactra
16 vaccine, n=1164; Menomune–A/C/Y/W-135 vaccine, n=1031) were enrolled at US sites, and
17 32% of participants at a Chilean site. The median ages in the Chilean and US subpopulations
18 were 5 and 6 years old, respectively. All adolescents and adults were enrolled at US sites. As the
19 route of administration differed for the two vaccines (Menactra vaccine given intramuscularly,
20 Menomune–A/C/Y/W-135 vaccine given subcutaneously), study personnel collecting the safety
21 data differed from personnel administering the vaccine. Solicited local and systemic reactions
22 were monitored daily for 7 days post-vaccination using a diary card. Participants were monitored

1 for 28 days for unsolicited adverse events and for 6 months post-vaccination for visits to an
2 emergency room, unexpected visits to an office physician, and serious adverse events.
3 Unsolicited adverse event information was obtained either by telephone interview or at an
4 interim clinic visit. Information regarding adverse events that occurred in the 6-month post-
5 vaccination time period was obtained via a scripted telephone interview. At least 94% of
6 participants from the three primary studies completed the 6-month follow-up evaluation.
7 In the two concomitant vaccination studies with Menactra and either Typhim Vi or Td vaccines,
8 local and systemic adverse events were monitored for 7 days post-vaccination using a diary card.
9 Serious adverse events occurring within 1 month after each vaccination were reported and
10 recorded.

11

12 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
13 observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical
14 trials of another vaccine and may not reflect the rates observed in practice. The adverse reaction
15 information from clinical trials does, however, provide a basis for identifying the adverse events
16 that appear to be related to vaccine use and for approximating rates of those events.

17

18 **Serious Adverse Events in All Safety Studies**

19 Serious adverse events reported within a 6-month time period following vaccination in children
20 2–10 years old occurred at a rate of 0.6% following Menactra vaccine and at a rate of 0.7%
21 following Menomune–A/C/Y/W-135 vaccine. Serious adverse events reported within a 6-month

1 time period following vaccination in adolescents and adults occurred at a rate of 1.0% following
2 Menactra vaccine and at a rate of 1.3% following Menomune–A/C/Y/W-135 vaccine.

3

4 **Solicited Adverse Events in the Primary Safety Studies**

5 The most frequently reported solicited local and systemic adverse reactions in US children aged
6 2–10 years (**Table 7**) were injection site pain and irritability. Diarrhea, drowsiness, and anorexia
7 were also common.

8

9 The most commonly reported solicited local and systemic adverse reactions in adolescents, ages
10 11–18 years (**Table 8**), and adults, ages 18–55 years (**Table 9**), were injection site pain,
11 headache and fatigue. Except for redness in adults, local reactions were more frequently reported
12 after Menactra vaccination than after Menomune–A/C/Y/W-135 vaccination. The majority of
13 local and systemic reactions following Menactra or Menomune–A/C/Y/W-135 vaccination were
14 reported as mild in intensity. Between the vaccine groups, differences in rates of malaise,
15 diarrhea, anorexia, vomiting, or rash, including urticaria were not statistically significant.

16

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

Reaction	Menactra vaccine *N=1157			Menomune–A/C/Y/W-135 vaccine *N=1027		
	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		

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

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

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

- 1 § Moderate: interferes with normal activities, Severe: disabling, unwilling to engage in play or interact with
 2 others.
- 3 || Moderate: 1-3 hours duration, Severe: >3 hours duration.
- 4 ¶ Moderate: Decreased range of motion due to pain or discomfort, Severe: unable to move major joints due
 5 to pain.
- 6 # Moderate: 3-4 episodes, Severe: ≥5 episodes.
- 7 ** Moderate: Skipped 2 meals, Severe: skipped ≥3 meals.
- 8 †† Oral equivalent temperature; Moderate: 38.4-39.4°C, Severe: ≥39.5°C.
- 9 ‡‡ Moderate: 2 episodes, Severe: ≥3 episodes.
- 10 §§ These solicited adverse events were reported as present or absent only.

11

12 **Table 8: Percentage of Participants 11–18 Years of Age Reporting Solicited Adverse**
 13 **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		

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

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

Reaction	Menactra vaccine N*=1371			Menomune–A/C/Y/W-135 vaccine N*=1159		
	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		

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

12

13 Adverse Events in Concomitant Vaccine Studies

14 Local and Systemic Reactions when Given with Td Vaccine

15 See [Concomitant Vaccine Administration](#) section for a description of the study design and

16 number of participants. The two vaccine groups reported similar frequencies of pain, induration,

17 redness and swelling at the Menactra injection site, as well as, at the Td injection site. Pain was

18 the most frequent local reaction reported at both the Menactra and Td injection sites. More

19 participants experienced pain after Td vaccination than after Menactra vaccination (71% versus

20 53%). The majority (66%-77%) of local solicited reactions for both groups at either injection site

21 were reported as mild and resolved within 3 days post-vaccination.

22

23 The overall rate of systemic adverse events was higher when Menactra and Td vaccines were

24 given concomitantly than when Menactra vaccine was administered 28 days after Td. In both

1 groups, the most common reactions were headache (Menactra vaccine + Td, 36%; Td + Placebo,
2 34%; Menactra vaccine alone, 22%) and fatigue (Menactra vaccine + Td, 32%; Td + Placebo,
3 29%; Menactra vaccine alone, 17%). Between the groups, differences in rates of malaise,
4 diarrhea, anorexia, vomiting, or rash were not statistically significant. Fever $\geq 40.0^{\circ}\text{C}$ occurred at
5 $\leq 0.5\%$ in all groups. No seizures occurred in either group.

6

7 Local and Systemic Reactions when Given with Typhim Vi Vaccine

8 See [Concomitant Vaccine Administration](#) section for a description of the study design and
9 number of participants. The two vaccine groups reported similar frequencies of pain, induration,
10 redness and swelling at the Menactra injection site, as well as, at the Typhim Vi injection site.
11 Pain was the most frequent local reaction reported at both the Menactra and Typhim Vi injection
12 sites. More participants experienced pain after Typhim Vi vaccination than after Menactra
13 vaccination (76% versus 47%). The majority (70%-77%) of local solicited reactions for both
14 groups at either injection site were reported as mild and resolved within 3 days post-vaccination. In
15 both groups, the most common systemic reaction was headache (Menactra + Typhim Vi vaccine,
16 41%; Typhim Vi vaccine + Placebo, 42%; Menactra vaccine alone, 33%) and fatigue (Menactra
17 + Typhim Vi vaccine, 38%; Typhim Vi vaccine + Placebo, 35%; Menactra vaccine alone, 27%).
18 Between the groups, differences in rates of malaise, diarrhea, anorexia, or vomiting were not
19 statistically significant. Fever $\geq 40.0^{\circ}\text{C}$ and seizures were not reported in either group.

20

21 Post-Marketing Reports

22 The following adverse events have been reported during post-approval use of Menactra vaccine.
23 Because these events were reported voluntarily from a population of uncertain size, it is not

1 always possible to reliably calculate their frequency or to establish a causal relationship to
2 Menactra vaccine exposure.

3

4 Immune System disorders - Hypersensitivity reactions such as anaphylactic/anaphylactoid
5 reaction, wheezing, difficulty breathing, upper airway swelling, urticaria, erythema, pruritus,
6 hypotension

7

8 Nervous system disorders - Guillain-Barré syndrome, vasovagal syncope, facial palsy,
9 transverse myelitis, acute disseminated encephalomyelitis

10

11 Musculoskeletal and connective tissue disorders - Myalgia

12

13 **Reporting of Adverse Events**

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

20

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

23

1 **DOSAGE AND ADMINISTRATION**

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

4

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

6

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

8

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

11

12 **Concomitant Administration with Other Vaccines**

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

22

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

3

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

6

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

10

11 **HOW SUPPLIED**

12 BD Luer-Lok® latex-free syringe, 0.5 mL (5 syringes per package). Product No. 49281-589-15

13 Vial, 1 Dose (5 vials per package). Product No. 49281-589-05

14

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

16

17 **STORAGE**

18 Store at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product that has been exposed to freezing

19 should not be used. Do not use after expiration date.

20

21

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1

2 Menactra vaccine is a registered trademark of Sanofi Pasteur Inc.

3

4 Product Information as of April 2008

5

6 Manufactured by:

7 **Sanofi Pasteur Inc.**

8 Swiftwater PA 18370 USA

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