

DATA SHEET

NAME OF THE MEDICINE

Menactra[®]

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

DESCRIPTION

Each 0.5 mL dose of vaccine contains:

Active ingredients:

- | | |
|---|---------------------------|
| • Meningococcal polysaccharide* Group A | 4.0 mcg/dose |
| • Meningococcal polysaccharide* Group C | 4.0 mcg/dose |
| • Meningococcal polysaccharide* Group Y | 4.0 mcg/dose |
| • Meningococcal polysaccharide* Group W-135 | 4.0 mcg/dose |
| • Diphtheria toxoid protein | Approximately 48 mcg/dose |

* Each of the four polysaccharides is conjugated to diphtheria toxoid.

Excipients:

- | | |
|---|----------|
| • Sodium chloride | 4.35 mg |
| (within 0.85% Physiological Saline [†] and 0.5M Phosphate Buffered Saline [§] , pH 6.8) | |
| • Sodium phosphate – dibasic anhydrous | 0.348 mg |
| (within 0.5M Phosphate Buffered Saline [§] , pH 6.8) | |
| • Sodium phosphate – monobasic | 0.352 mg |
| (within 0.5M Phosphate Buffered Saline [§] , pH 6.8) | |

[†] 0.85% Physiological Saline is composed of sodium chloride in Water for Injections.

[§] 0.5M Phosphate Buffered Saline is composed of sodium chloride, sodium phosphate dibasic anhydrous and sodium phosphate monobasic in Water for Injections.

Menactra vaccine is a sterile, clear to slightly turbid solution of *Neisseria meningitidis* purified capsular polysaccharides of groups A, C, Y and W-135, individually conjugated to a carrier protein. The protein is a purified *Corynebacterium diphtheriae* toxoid, formalin-detoxified. Each

0.5 mL dose of vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution. No preservative or adjuvant is added.

There is no latex in any component of the vial.

PHARMACOLOGY

Mechanism of action

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

CLINICAL TRIALS

Immunogenicity

Individuals 9 months through 55 years of Age

The immunogenicity of Menactra vaccine has been studied in three clinical trials in infants 9 through 18 months of age, in four clinical trials among children 2 through 10 years of age, and in six clinical trials among adolescents and adults 11 through 55 years of age.

In approximately 2250 infants 9 through 18 months of age where one or two doses were administered either alone or with concomitant paediatric vaccine(s) (Measles, Mumps, Rubella and Varicella Virus vaccine Live [MMRV] or Pneumococcal 7-valent Conjugate (Diphtheria CRM197 Protein) vaccine [PCV7]). A subset of the participants in these trials received Menactra vaccine concomitantly with MMRV + *Haemophilus Influenza* type b vaccine [Hib].

Immunogenicity was evaluated in three comparative, randomised, US, multi-centre, 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.

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.

The Serum Bactericidal Assay (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).

The response to vaccination following one or two doses of vaccine administered to children 9 through 18 months of age and following one dose of vaccine administered to children 2 through 10 years of age was evaluated by the proportion of subjects having an SBA-H antibody titre of 1:8 or greater, for each serogroup. In individuals 11 through 55 years of age, the response to

vaccination with a single dose of vaccine 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. For individuals 2 through 55 years of age, vaccine efficacy was inferred from the demonstration of immunologic equivalence to a meningococcal polysaccharide vaccine, Menomune[®]-A/C/Y/W-135, Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined as assessed by SBA.

Children 9 through 23 Months of Age

In a randomised, US, multi-centre trial, children received Menactra vaccine at 9 months and 12 months of age. The first Menactra dose was administered alone, followed by a second Menactra vaccine dose given alone (N=404), or with MMRV (N=302), or with PCV7 (N=422). For all participants, sera were obtained approximately 30 days after last vaccination. There were no substantive differences in demographic characteristics between the vaccine groups. The median age range for administration of the first dose of Menactra was 278-279 days of age.

Table 1: Bactericidal Antibody Responses^a 30 Days Following a Second Dose of Menactra Vaccine Administered Alone or Concomitantly Administered with MMRV or PCV7 Vaccines at 12 Months of Age

		Vaccinations administered at 12 months of age following a dose of Menactra at 9 months of age					
		Menactra vaccine		Menactra + MMRV vaccines		Menactra + PCV7 vaccines	
		(N=272-277) ^b		(N=177-180) ^b		(N=264-267) ^b	
Serogroup			(95% CI) ^c		(95% CI) ^c		(95% CI) ^c
A	% ≥1:8 ^d	95.6	(92.4; 97.7)	92.7	(87.8; 96.0)	90.5	(86.3; 93.8)
	GMT	54.9	(46.8; 64.5)	52.0	(41.8; 64.7)	41.0	(34.6; 48.5)
C	% ≥1:8 ^d	100.0	(98.7; 100.0)	98.9	(96.0; 99.9)	97.8	(95.2; 99.2)
	GMT	141.8	(123.5; 162.9)	161.9	(136.3; 192.3)	109.5	(94.1; 127.5)
Y	% ≥1:8 ^d	96.4	(93.4; 98.2)	96.6	(92.8; 98.8)	95.1	(91.8; 97.4)
	GMT	52.4	(45.4; 60.6)	60.2	(50.4; 71.7)	39.9	(34.4; 46.2)
W-135	% ≥1:8 ^d	86.4	(81.8; 90.3)	88.2	(82.5; 92.5)	81.2	(76.0; 85.7)
	GMT	24.3	(20.8; 28.3)	27.9	(22.7; 34.3)	17.9	(15.2; 21.0)

^a Serum Bactericidal Assay with an exogenous human complement (SBA-H) source.

^b N=Number of participants with at least one valid serology result from a blood sample obtained between Days 30 to 44 post vaccination.

^c 95% CIs for the proportions are calculated based on the Clopper-Pearson Exact method and normal approximation for that of the GMTs.

^d The proportion of participants achieving at least an SBA-H titre of 1:8 thirty days after the second dose of Menactra.

Administration of Menactra to children at 12 months and 15 months of age was evaluated in a US study. Prior to the first dose, 33.3% [n=16/48] of participants had an hSBA titre ≥ 1:8 to Serogroup A, and 0-2% [n=0-1 of 50-51] to Serogroups C, Y and W-135. After the second dose, percentages of participants with an hSBA titre ≥ 1:8 were: 85.2%, Serogroup A [n=46/54];

100.0%, Serogroup C [n=54/54]; 96.3%, Serogroup Y [n=52/54]; 96.2%, Serogroup W-135 [n=50/52].

Immunogenicity in Children 2 through 10 Years of Age

Of 1408 enrolled children 2 through 10 years of age, 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 2** and **Table 3**).

Table 2: Comparison of Bactericidal Antibody Responses^a 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 ^b =48-52		Menomune–A/C/Y/W-135 vaccine N ^b =50-53	
Serogroup			(95% CI) ^c		(95% CI) ^c
A	% ≥ 1:8 ^d	73	(59, 84)	64	(50, 77)
	GMT	10	(8, 13)	10	(7, 12)
C	% ≥ 1:8 ^d	63	(48, 76)	38	(25, 53)
	GMT	27	(14, 52)	11	(5, 21)
Y	% ≥ 1:8 ^d	88	(75, 95)	73	(59, 84)
	GMT	51	(31, 84)	18	(11, 27)
W-135	% ≥ 1:8 ^d	63	(47, 76)	33	(20, 47)
	GMT	15	(9, 25)	5	(3, 6)

^a Serum Bactericidal Assay with an exogenous human complement (SBA-H) source.

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

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

^d The proportion of participants achieving at least an SBA-H titre of 1:8 was assessed using a 10% non-inferiority margin and a one-sided Type 1 error rate of 0.025.

Table 3: Comparison of Bactericidal Antibody Responses^a 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 ^b =84		Menomune–A/C/Y/W-135 vaccine N ^b =84	
Serogroup			(95% CI) ^c		(95% CI) ^c
A	% ≥ 1:8 ^d	81	(71, 89)	55	(44, 66)
	GMT	19	(14, 26)	7	(6, 9)
C	% ≥ 1:8 ^d	79	(68, 87)	48	(37, 59)
	GMT	28	(19, 41)	12	(7, 18)
Y	% ≥ 1:8 ^d	99	(94, 100)	92	(84, 97)
	GMT	99	(75, 132)	46	(33, 66)
W-135	% ≥ 1:8 ^d	85	(75, 92)	79	(68, 87)
	GMT	24	(18, 33)	20	(14, 27)

^a Serum Bactericidal Assay with an exogenous human complement (SBA-H) source.

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

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

^d The proportion of participants achieving at least an SBA-H titre of 1:8 was assessed using a 10% non-inferiority margin and a one-sided Type 1 error rate of 0.025.

In the subset of participants 2 through 3 years of age with undetectable pre-vaccination titres (i.e., < 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 through 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 11 through 18 years of Age

Results from the comparative clinical trial conducted in 881 adolescents aged 11 through 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 4**).

Table 4: Comparison of Bactericidal Antibody Responses^a to Menactra Vaccine and Menomune–A/C/Y/W-135 Vaccine 28 Days after Vaccination for Participants Aged 11–18 Years

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

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

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

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

^d 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 titre 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.

In participants with undetectable pre-vaccination titres (i.e., less than 8 at Day 0), seroconversion rates (defined as a ≥ 4-fold rise in Day 28 SBA titres) 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 18 through 55 years of Age

Results from the comparative clinical trial conducted in 2554 adults aged 18 through 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 5**).

Table 5: Comparison of Bactericidal Antibody Responses^a to Menactra Vaccine and Menomune–A/C/Y/W-135 Vaccine 28 Days After Vaccination for Participants Aged 18–55 Years

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

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

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

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

^d 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 titre 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.

In participants with undetectable pre-vaccination titres (i.e., less than 8 at Day 0), seroconversion rates (defined as a ≥ 4-fold rise in Day 28 SBA titres) 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

MMRV (or MMR + V) or PCV7

In a US, active-controlled trial, 1179 children received Menactra vaccine at 9 months and 12 months of age. At 12 months of age these children received Menactra concomitantly with MMRV (N=616), or MMR + V (N=48), or PCV7 (N=250). Another group of 12-month old children received MMRV + PCV7 (N=485). Sera were obtained approximately 30 days after the last vaccinations. Measles, mumps, rubella and varicella antibody responses among children who

received Menactra vaccine and MMRV (or MMR and V) were comparable to corresponding antibody responses among children who received MMRV and PCV7.

When Menactra was given concomitantly with PCV7, the non-inferiority criteria for comparisons of pneumococcal IgG GMCs (upper limit of the two-sided 95% CI of the GMC ratio ≤ 2) were not met for 3 of 7 serotypes (4, 6B, 18C). In a subset of subjects with available sera, pneumococcal opsonophagocytic assay GMT data were consistent with IgG GMC data.

Tetanus and Diphtheria

The concomitant use of Menactra vaccine and Tetanus and Diphtheria Toxoids Adsorbed, For Adult Use (Td, manufactured by Sanofi Pasteur Inc) was evaluated in a double-blind, randomised, controlled clinical trial conducted in 1021 participants aged 11–17 years. For meningococcal serogroups C, Y and W-135, the proportion of participants with a 4-fold or greater rise in SBA titre 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.

Typhoid Vi Polysaccharide Vaccine, Typhim Vi®

The concomitant use of Menactra vaccine and Typhim Vi vaccine (recommended for certain travellers) was evaluated in a double-blind, randomised, controlled clinical trial conducted in 945 participants aged 18–55 years. 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.

INDICATIONS

Menactra vaccine is indicated for active immunisation in individuals from 9 months 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 immunisation against diphtheria.

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, are contraindications to vaccine administration.

Vaccination must be postponed in case of febrile or acute disease. However a minor febrile or non-febrile illness, such as mild upper respiratory infection, is not usually a reason to postpone immunisation.

PRECAUTIONS

Do not administer by intravascular injection: ensure that the needle does not penetrate a blood vessel.

Prior to Vaccination

Anaphylaxis

As with all injectable vaccines, appropriate medical treatment and supervision should be readily available for immediate use in case of a rare anaphylactic reaction following the administration of vaccine. As a precautionary measure, adrenaline injection (1:1000) and other appropriate agents and equipment must be immediately available in case of anaphylactic or serious allergic reactions.

Individual History

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

Syncope has been reported following vaccination with Menactra. Procedures should be in place to prevent falling injury and manage syncopal reactions.

Special Patient Groups

Thrombocytopaenia or Bleeding Disorders

Menactra vaccine has not been evaluated in individuals with thrombocytopaenia or bleeding disorders. As with any other vaccine administered intramuscularly, the vaccine risk versus benefit for individuals at risk of haemorrhage following intramuscular injection must be evaluated. If the decision is made to administer any product by intramuscular injection to such individuals, it should be given with caution, with steps taken to avoid the risk of haematoma formation following injection.

Immunosuppression

Menactra vaccine has been evaluated in about 300 Human Immunodeficiency Virus (HIV)-infected subjects. Menactra vaccine was safe and immunogenic in this population. The immune response to Menactra vaccine administered to other immunosuppressed persons has not been

studied. If the vaccine is used in individuals under immunosuppressive therapy, the expected immune response may not be obtained.

Guillain-Barre Syndrome

Persons previously diagnosed with Guillain-Barré syndrome (GBS) may be at increased risk of GBS following receipt of Menactra vaccine. The decision to give Menactra vaccine should take into account the potential benefits and risks.

GBS has been reported in temporal relationship following administration of Menactra vaccine. The risk of GBS following Menactra vaccination was evaluated in a post-marketing retrospective cohort study. (see **ADVERSE EFFECTS**)

Protection

Menactra vaccine may not protect 100% of individuals.

Menactra vaccine will only protect against *N meningitidis* A, C, Y and W-135 serogroups and will not protect against any other microorganisms.

Although an antibody response to diphtheria toxoid may occur, Menactra vaccine should not be considered as an immunising agent against diphtheria. No changes in the schedule for administering routine vaccines containing diphtheria toxoid are recommended.

Effects on fertility

There were no effects on the mating performance or fertility of female mice intramuscularly injected with Menactra vaccine (at one fifth of the clinical dose) two weeks prior to mating. The effect of Menactra vaccine on male fertility has not been evaluated (see also Use in Pregnancy).

Use in Pregnancy (Category B2)

In female mice intramuscularly injected with Menactra vaccine (at one fifth of the clinical dose) two weeks prior to mating and on gestation days 6 and 18, there were no significant toxicological effects in the dams, their foetuses or pups. Adequate human data on the use of Menactra vaccine during pregnancy are limited. The vaccine should be used during pregnancy only when clearly needed, such as during an outbreak or prior to necessary travel to an endemic area, and only following an assessment of the risks and benefits.

Sanofi Pasteur maintains a pregnancy registry to monitor foetal outcomes of pregnant women exposed to Menactra vaccine. Healthcare providers are encouraged to inform sanofi pasteur of any pregnant women who receive Menactra vaccine for their inclusion in the vaccination pregnancy registry by calling 1800 829 468 (in Australia) or 0800 283 684 (in New Zealand).

Use in Lactation

It is not known whether the active substances included in the vaccine are excreted in human milk, but antibodies to the polysaccharides have been found to be transferred to the suckling offspring of mice.

Animal studies conducted in mice have not shown any harmful effect on the postnatal development of offspring exposed through breastfeeding to Menactra-induced maternal antibodies. However, the effect on breast-fed infants of the administration of Menactra to their mothers has not been studied. The risks and benefits of vaccination should be assessed before making the decision to immunise a nursing woman.

Paediatric Use

Safety and effectiveness of Menactra vaccine in children below the age of 9 months have not been established.

Use in the Elderly

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

Genotoxicity

No genotoxicity studies have been conducted with Menactra vaccine.

Carcinogenicity

No carcinogenicity studies have been conducted with Menactra vaccine.

Effect on Laboratory Tests

Interference of Menactra with laboratory tests has not been studied.

INTERACTIONS WITH OTHER MEDICINES

For information regarding concomitant administration of Menactra vaccine with other vaccines, see **CLINICAL TRIALS** and **ADVERSE EFFECTS** sections.

If the vaccine is used in individuals under immunosuppressive therapy, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), the expected immune response may not be obtained.

Menactra must not be mixed with any vaccine in the same syringe. Separate injection sites should be used in case of concomitant administration.

ADVERSE EFFECTS

Clinical Trials Experience

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.

Children 9 Through 18 Months of Age

The safety of Menactra vaccine was evaluated in four clinical studies that enrolled 3721 participants who received Menactra vaccine at 9 through 18 months of age. At 12 months of age these children also received one or more other recommended vaccines [MMRV or MMR and Varicella Virus Vaccine Live (V), PCV7, Hepatitis A Vaccine (HepA)]. A control group of 997 children was enrolled at 12 months of age and received two or more childhood vaccines [MMRV (or MMR + V), PCV7, HepA] at 12 months of age [see **CLINICAL TRIALS**, Concomitant Vaccine Administration]. Three percent of individuals received MMR and V, instead of MMRV, at 12 months of age.

The primary safety study was a controlled trial that enrolled 1256 children who received Menactra vaccine at 9 and 12 months of age. At 12 months of age these children received MMRV (or MMR + V), PCV7 and HepA. A control group of 522 children received MMRV, PCV7 and HepA. Of the 1778 children, 78% of participants (Menactra vaccine, N=1056; control group, N=322) were enrolled at United States (US) sites and 22% at a Chilean site. (Menactra vaccine, N=200; control group, N=200).

Individuals 2 Through 55 years of Age

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. The three primary safety studies were randomised, active-controlled trials that enrolled participants 2–10, 11–18 and 18–55 years of age, respectively.

Serious Adverse Events in All Safety Studies

Serious adverse events (SAEs) reported within a 6-month time period following vaccination in individuals 9 months through 55 years of age. In children who received Menactra vaccine at 9 months and at 12 months of age, SAEs occurred at a rate of 2.0% - 2.5%. In participants who received one or more childhood vaccine(s) (without co-administration of Menactra vaccine) at 12 months of age, SAEs occurred at a rate of 1.6% - 3.6%, depending on the number and type of

vaccines received. In children 2–10 years of age, SAEs 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. In adolescents 11–18 years of age and adults 18–55 years of age, SAEs 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 injection site and systemic adverse reactions within 7 days following vaccination in children 9 months and 12 months of age (**Table 6**) were injection site tenderness and irritability.

The most frequently reported solicited local and systemic adverse reactions in children aged 2–10 years (**Table 7**) were injection site pain, irritability, diarrhoea, drowsiness, and anorexia respectively. In adolescents, ages 11–18 years (**Table 8**), and adults, ages 18–55 years (**Table 9**) the most commonly reported 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.

Table 6: Percentage of US Participants Reporting Solicited Adverse Reactions Within 7 Days Following Vaccine Administration at 9 Months and 12 Months of Age

	Menactra vaccine at 9 months of age			Menactra + PCV7 ^a + MMRV ^b + HepA ^c vaccines at 12 months of age			PCV7 ^a + MMRV ^b + HepA ^c vaccines at 12 months of age		
	N ^d =998 - 1002			N ^d =898 - 908			N ^d =302 - 307		
Reaction	Any	Grade 2	Grade 3	Any	Grade 2	Grade 3	Any	Grade 2	Grade 3
Local/Injection Site									
Tenderness^e									
Menactra Site	37.4	4.3	0.6	48.5	7.5	1.3	-	-	-
PCV7 Site	-	-	-	45.6	9.4	1.6	45.7	8.3	0.3
MMRV Site	-	-	-	38.9	7.1	1.0	43.0	5.2	0.0
HepA Site	-	-	-	43.4	8.7	1.4	40.9	4.6	0.3
Erythema^f									
Menactra Site	30.2	2.5	0.3	30.1	1.3	0.1	-	-	-
PCV7 Site	-	-	-	29.4	2.6	0.2	32.6	3.0	0.7
MMRV Site	-	-	-	22.5	0.9	0.3	33.2	5.9	0.0
HepA Site	-	-	-	25.1	1.1	0.0	26.6	0.7	0.0

Swelling ^f									
Menactra Site	16.8	0.9	0.2	16.2	0.9	0.1	-	-	-
PCV7 Site	-	-	-	19.5	1.3	0.4	16.6	1.3	0.7
MMRV Site	-	-	-	12.1	0.4	0.1	14.1	0.3	0.0
HepA Site	-	-	-	16.4	0.7	0.2	13.5	0.0	0.3
Systemic									
Irritability ^g	56.8	23.1	2.9	62.1	25.7	3.7	64.8	28.7	4.2
Abnormal crying ^h	33.3	8.3	2.0	40.0	11.5	2.4	39.4	10.1	0.7
Drowsiness ⁱ	30.2	3.5	0.7	39.8	5.3	1.1	39.1	5.2	0.7
Appetite loss ^j	30.2	7.1	1.2	35.7	7.6	2.6	31.9	6.5	0.7
Vomiting ^k	14.1	4.6	0.3	11.0	4.4	0.2	9.8	2.0	0.0
Fever ^l	12.2	4.5	1.1	24.5	11.9	2.2	21.8	7.3	2.6

^a PCV7 (Pneumovax[®]) = Pneumococcal 7-valent Conjugate Vaccine

^b MMRV (ProQuad[®]) = Measles, Mumps, Rubella and Varicella Virus Vaccine Live

^c HepA (VAQTA[®]) = Hepatitis A Vaccine, Inactivated

^d N = The number of subjects with available data.

^e Grade 2: cries and protests when injection site is touched, Grade 3: cries when injected limb is moved, or the movement of the injected limb is reduced.

^f Grade 2: ≥1.0 inches to <2.0 inches, Grade 3: ≥2.0 inches.

^g Grade 2: requires increased attention, Grade 3: inconsolable.

^h Grade 2: 1 to 3 hours, Grade 3: >3 hours.

ⁱ Grade 2: not interested in surroundings or did not wake up for a feed/meal, Grade 3: sleeping most of the time or difficult to wake up.

^j Grade 2: missed 1 or 2 feeds/meals completely, Grade 3: refuses ≥3 feeds/meals or refuses most feeds/meals.

^k Grade 2: 2 to 5 episodes per 24 hours, Grade 3: ≥6 episodes per 24 hours or requiring parenteral hydration.

^l Grade 2: >38.5°C to ≤39.5°C, Grade 3: >39.5°C.

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

	Menactra vaccine ^a N=1157			Menomune–A/C/Y/W-135 vaccine ^a N=1027		
Reaction	Any	Grade 2	Grade 3	Any	Grade 2	Grade 3
Redness ^c	21.8	4.6	3.9	7.9	0.5	0.0
Swelling ^c	17.4	3.9	1.9	2.8	0.3	0.0
Induration ^c	18.9	3.4	1.4	4.2	0.6	0.0
Pain ^b	45.0	4.9	0.3	26.1	2.5	0.0
Drowsiness ^f	10.8	2.7	0.3	11.2	2.5	0.5

Irritability ^d	12.4	3.0	0.3	12.2	2.6	0.6
Arthralgia ^h	6.8	0.5	0.2	5.3	0.7	0.0
Diarrhoea ^e	11.1	2.1	0.2	11.8	2.5	0.3
Anorexia ^g	8.2	1.7	0.4	8.7	1.3	0.8
Fever ⁱ	5.2	1.7	0.3	5.2	1.7	0.2
Vomiting ^k	3.0	0.7	0.3	2.7	0.7	0.6
Rash ^j	3.4			3.0		
Seizure ^j	0.0			0.0		

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

^b Grade 2: interferes with normal activities, Grade 3: disabling, unwilling to move arm.

^c Grade 2: 1.0-2.0 inches, Grade 3: >2.0 inches.

^d Grade 2: 1-3 hours duration, Grade 3: >3 hours duration.

^e Grade 2: 3-4 episodes, Grade 3: ≥5 episodes.

^f Grade 2: interferes with normal activities, Grade 3: disabling, unwilling to engage in play or interact with others.

^g Grade 2: skipped 2 meals, Grade 3: skipped ≥3 meals.

^h Grade 2: decreased range of motion due to pain or discomfort, Grade 3: unable to move major joints due to pain.

ⁱ Oral equivalent temperature; Grade 2: 38.4°C to 39.4°C, Grade 3: ≥39.5°C.

^j These solicited adverse events were reported as present or absent only.

^k Grade 2: 2 episodes, Grade 3: ≥3 episodes.

Note: During the study Grade 1, Grade 2, and Grade 3 were collected as Mild, Moderate, and Severe respectively.

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

	Menactra vaccine N ^a =2264			Menomune–A/C/Y/W-135 vaccine N ^a =970		
Reaction	Any	Grade 2	Grade 3	Any	Grade 2	Grade 3
Redness ^d	10.9 ^c	1.6 ^c	0.6 ^c	5.7	0.4	0.0
Swelling ^d	10.8 ^c	1.9 ^c	0.5 ^c	3.6	0.3	0.0
Induration ^d	15.7 ^c	2.5 ^c	0.3	5.2	0.5	0.0
Pain ^b	59.2 ^c	12.8 ^c	0.3	28.7	2.6	0.0
Headache ^e	35.6 ^c	9.6 ^c	1.1	29.3	6.5	0.4
Fatigue ^e	30.0 ^c	7.5	1.1 ^c	25.1	6.2	0.2
Malaise ^e	21.9 ^c	5.8 ^c	1.1	16.8	3.4	0.4
Arthralgia ^e	17.4 ^c	3.6 ^c	0.4	10.2	2.1	0.1
Diarrhoea ^f	12.0	1.6	0.3	10.2	1.3	0.0
Anorexia ^g	10.7 ^c	2.0	0.3	7.7	1.1	0.2
Chills ^c	7.0 ^c	1.7 ^c	0.2	3.5	0.4	0.1

Fever ^h	5.1 ^c	0.6	0.0	3.0	0.3	0.1
Vomiting ⁱ	1.9	0.4	0.3	1.4	0.5	0.3
Rash ^j	1.6			1.4		
Seizure ^j	0.0			0.0		

^a N = The number of subjects with available data.

^b Grade 2: interferes with or limits usual arm movement, Grade 3: disabling, unable to move arm.

^c Denotes $p < 0.05$ level of significance. The p -values were calculated for each category and severity using Chi Square test.

^d Grade 2: 1.0-2.0 inches, Grade 3: >2.0 inches.

^e Grade 2: interferes with normal activities, Grade 3: requiring bed rest.

^f Grade 2: 3-4 episodes, Grade 3: ≥ 5 episodes.

^g Grade 2: skipped 2 meals, Grade 3: skipped ≥ 3 meals.

^h Oral equivalent temperature; Grade 2: 38.5°C to 39.4°C, Grade 3: $\geq 39.5^\circ\text{C}$.

ⁱ Grade 2: 2 episodes, Grade 3: ≥ 3 episodes.

^j These solicited adverse events were reported as present or absent only.

Note: During the study Grade 1, Grade 2, and Grade 3 were collected as Mild, Moderate, and Severe respectively.

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

Reaction	Menactra vaccine N ^a =1371			Menomune–A/C/Y/W-135 vaccine N ^a =1159		
	Any	Grade 2	Grade 3	Any	Grade 2	Grade 3
Redness ^d	14.4	2.9	1.1 ^c	16.0	1.9	0.1
Swelling ^d	12.6 ^c	2.3 ^c	0.9 ^c	7.6	0.7	0.0
Induration ^d	17.1 ^c	3.4 ^c	0.7 ^c	11.0	1.0	0.0
Pain ^b	53.9 ^c	11.3 ^c	0.2	48.1	3.3	0.1
Headache ^e	41.4	10.1	1.2	41.8	8.9	0.9
Fatigue ^e	34.7	8.3	0.9	32.3	6.6	0.4
Malaise ^e	23.6	6.6 ^c	1.1	22.3	4.7	0.9
Arthralgia ^e	19.8 ^c	4.7 ^c	0.3	16.0	2.6	0.1
Diarrhoea ^f	16.0	2.6	0.4	14.0	2.9	0.3
Anorexia ^g	11.8	2.3	0.4	9.9	1.6	0.4
Chills ^e	9.7 ^c	2.1 ^c	0.6 ^c	5.6	1.0	0.0
Fever ⁱ	1.5 ^c	0.3	0.0	0.5	0.1	0.0
Vomiting ^h	2.3	0.4	0.2	1.5	0.2	0.4
Rash ^j	1.4			0.8		
Seizure ^j	0.0			0.0		

^a N = The number of subjects with available data.

^b Grade 2: interferes with or limits usual arm movement, Grade 3: disabling, unable to move arm.

^c Denotes $p < 0.05$ level of significance. The p -values were calculated for each category and severity using Chi Square test.

^d Grade 2: 1.0-2.0 inches, Grade 3: >2.0 inches.

^e Grade 2: interferes with normal activities, Grade 3: requiring bed rest.

^f Grade 2: 3-4 episodes, Grade 3: ≥ 5 episodes.

^g Grade 2: skipped 2 meals, Grade 3: skipped ≥ 3 meals.

^h Grade 2: 2 episodes, Grade 3: ≥ 3 episodes.

ⁱ Oral equivalent temperature; Grade 2: 39.0°C to 39.9°C, Grade 3: $\geq 40.0^\circ\text{C}$.

^j These solicited adverse events were reported as present or absent only.

Note: During the study Grade 1, Grade 2, and Grade 3 were collected as Mild, Moderate, and Severe respectively.

Adverse Events in Concomitant Vaccine Studies

Solicited Injection site and Systemic Reactions when Given with Routine Paediatric Vaccines

For a description of the study design and number of participants [see **CLINICAL TRIALS**, Concomitant Vaccine Administration]. In the primary safety study, 1378 US children were enrolled to receive Menactra vaccine alone at 9 months of age and Menactra vaccine plus one or more other routinely administered vaccines (MMRV, PCV7 and HepA) at 12 months of age (N=961). Another group of children received two or more routinely administered vaccines (MMRV, PCV7 and HepA vaccines) (control group, n=321) at 12 months of age. The frequency of occurrence of solicited adverse events is presented in Table 5. Participants who received Menactra vaccine and the concomitant vaccines at 12 months of age described above reported similar frequencies of tenderness, redness and swelling at the Menactra vaccine injection site and at the concomitant vaccine injection sites. Tenderness was the most frequent injection site reaction (48%, 39%, 46% and 43% at the Menactra vaccine, MMRV, PCV7 and HepA vaccine sites, respectively). Irritability was the most frequent systemic reaction, reported in 62% of recipients of Menactra vaccine plus concomitant vaccines, and 65% of control group. [See **CLINICAL TRIALS**, Concomitant Vaccine Administration].

Local and Systemic Reactions when Given with Td Vaccine

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.

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 and fatigue.

Local and Systemic Reactions when Given with Typhim Vi Vaccine

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 and fatigue.

Post-Marketing Reports

Based on spontaneous reporting, the following additional adverse events have been reported during the commercial use of Menactra vaccine. These events have been very rarely reported. However, 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.

Immune system disorders:

Hypersensitivity reactions such as anaphylaxis/anaphylactic reaction, wheezing, difficulty breathing, upper airway swelling, urticaria, erythema, pruritus, hypotension

Nervous system disorders:

Guillain-Barré syndrome, paraesthesia, vasovagal syncope, dizziness, convulsion, facial palsy, acute disseminated encephalomyelitis, transverse myelitis

Musculoskeletal and connective tissue disorders:

Myalgia

Post-marketing Safety Study

The risk of GBS following receipt of Menactra vaccine was evaluated in a US retrospective cohort study using healthcare claims data from 9,578,688 individuals 11 through 18 years of age, of whom 1,431,906 (15%) received Menactra vaccine. Of 72 medical chart-confirmed GBS cases, none had received Menactra vaccine within 42 days prior to symptom onset. An additional 129 potential cases of GBS could not be confirmed or excluded due to absent or insufficient medical chart information. In an analysis that took into account the missing data, estimates of the attributable risk of GBS ranged from 0 to 5 additional cases of GBS per 1,000,000 vaccinees within the 6 week period following vaccination.

DOSAGE AND ADMINISTRATION

Menactra vaccine should be administered as a single 0.5 mL injection by the **intramuscular** route, preferably in the anterolateral thigh or deltoid region depending on the individual's age and muscle mass.

In children 9 through 23 months of age, Menactra vaccine is given as a 2-dose series at least three months apart.

Individuals 2 through 55 years of age receive a single dose.

Do not administer by intravascular injection.

Avoid injecting the vaccine intradermally or subcutaneously since clinical studies have not been conducted to establish safety and efficacy of the vaccine using these routes of administration.

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

There are limited data available on the length of time that should lapse before administration of Menactra vaccine in those individuals who have been previously vaccinated with other meningococcal vaccines.

For further information, refer to the current National Immunisation Handbook.

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

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.

Product is for single use in one patient only. Discard any residue.

OVERDOSE

No case of overdose has been reported.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Vial, 1 Dose

Packs of 1 vial (marketed) or 5 vials (not marketed)

Storage

Store at 2°C to 8°C (Refrigerate. Do not freeze). Product that has been exposed to freezing should not be used. Do not use after expiration date.

Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Australia:

sanofi-aventis australia pty ltd

Talavera Corporate Centre – Building D

12-24 Talavera Road

Macquarie Park NSW 2113

Australia

Tel: 1800 829 468

New Zealand:

sanofi-aventis new zealand pty ltd

Level 8, James & Wells Tower

56 Cawley St

Ellerslie

Auckland

New Zealand

Tel: 0800 727 838

POISON SCHEDULE OF THE MEDICINE

S4 Prescription Only Medicine

DATE OF MOST RECENT AMENDMENT

29 April 2015

Menactra[®] is a registered trademark of sanofi pasteur and its subsidiaries.