PRODUCT MONOGRAPH

Menactra®

Meningococcal (Groups A, C, Y and W-135) Polysaccharide

Diphtheria Toxoid Conjugate Vaccine

Solution for Injection

Active Immunizing Agent for the Prevention of Meningococcal Disease

ATC Code: J07AH

Sanofi Pasteur Limited

Toronto, Ontario, Canada

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Menactra®

Meningococcal (Groups A, C, Y and W-135) Polysaccharide

Diphtheria Toxoid Conjugate Vaccine

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration

Intramuscular injection

Dosage Form / Strength

Solution for injection.

Each 0.5 mL dose is formulated to contain:

Active Ingredients

4 µg each of meningococcal A, C, Y and W-135 polysaccharides conjugated to a total of approximately 48 µg of a diphtheria toxoid protein carrier.

Clinically Relevant Non-medicinal Ingredients

N/A

For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING.

DESCRIPTION

Menactra® [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] is a sterile, clear to slightly turbid liquid containing *Neisseria meningitidis* serogroups A, C, Y and W-135 capsular polysaccharide antigens individually conjugated to diphtheria toxoid protein. The 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.

INDICATIONS AND CLINICAL USE

Menactra® is indicated for active immunization for the prevention of invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, Y and W-135 in persons 9 months through 55 years of age.

CONTRAINDICATIONS

Hypersensitivity

Known systemic hypersensitivity reaction to any component of Menactra® or its container or a life-threatening reaction after previous administration of a vaccine containing similar components are contraindications to vaccination. (See SUMMARY PRODUCT INFORMATION.) The National Advisory Committee on Immunization (NACI) recommends that such persons may be referred to an allergist for evaluation if immunizations are considered. (1)

WARNINGS AND PRECAUTIONS

General

Before administration of Menactra®, health-care providers should inform the recipient or the parent or guardian of the recipient of the benefits and risks of immunization, inquire about the recent health status of the recipient, review the recipient's history concerning possible hypersensitivity to the vaccine or similar vaccine, previous immunization history, the presence of any contraindications to immunization and comply with any local requirements regarding information to be provided to the recipient/guardian before immunization.

It is extremely important that the recipient, parent or guardian be questioned concerning any signs or symptoms of an adverse reaction after a previous dose of vaccine containing similar components. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)

Protection

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

Menactra® is not indicated for the prevention of invasive meningococcal disease caused by serogroup B and is not to be used for the treatment of meningococcal infections.

Menactra® vaccination is not indicated for immunization against diphtheria.

As with any vaccine, vaccination with Menactra® may not protect 100% of individuals against vaccine serogroups.

Administration Route Related Precautions:

The subcutaneous routes of administration should not be utilized. There have been reports of subcutaneous use of Menactra®, and the safety profile associated with these reports did not differ from that observed with intramuscular use of Menactra®.

Do not administer Menactra® intravenously or subcutaneously.

Menactra® should not be administered into the buttocks.

Febrile and Acute Disease:

Vaccination should be postponed in cases of acute or febrile disease. (2) However, a disease with low-grade fever should not usually be a reason to postpone vaccination.

Hematologic

Menactra® has not been evaluated in persons with thrombocytopenia or bleeding disorders. As with any other vaccine administered intramuscularly, the vaccine risk versus benefit for persons at risk of hemorrhage following intramuscular injection must be evaluated. NACI has published recommendations for the immunization of people with hemophilia and other bleeding disorders. (1)

Immune

The possibility of allergic reactions in persons sensitive to components of the vaccine should be evaluated. Hypersensitivity reactions may occur following the use of Menactra® even in persons with no prior history of hypersensitivity to the product components.

As with all products, epinephrine hydrochloride solution (1:1,000) and other appropriate agents should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.

Individuals with functional or anatomical asplenia may produce an immune response to Menactra®, however, the degree of protection that would be afforded is unknown.

Immunocompromised persons (whether from disease or treatment) may not achieve the expected immune response. If possible, consideration should be given to delaying vaccination until after the completion of any immunosuppressive treatment. Nevertheless, NACI and ACIP recommend vaccination of persons with chronic immunodeficiency such as HIV infection even if the immune response might be limited. (1)

Neurologic

Guillain-Barré syndrome (GBS) has been very rarely reported in temporal relationship following administration of Menactra®. (3) A recent large multi-site retrospective cohort and nested case-control study, found no evidence of increased GBS risk associated with the use of Menactra®. (4)

Persons previously diagnosed with GBS may be at increased risk of GBS following receipt of Menactra®. The decision to give Menactra should take into account the potential benefits and risks.

Pregnant Women

Animal reproduction studies (5) have not demonstrated a risk with respect to effects on pregnancy and embryo-fetal development, parturition and postnatal development. However, since there are no data on the use of this vaccine in pregnant women, Menactra® should be given to a pregnant woman only if 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.

Nursing Women

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. (5)

Animal studies conducted in mice have not shown any harmful effect on offspring postnatal development caused by maternal antibodies induced by the vaccine. (5) 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 immunize a nursing woman.

Geriatrics

Clinical data are available in persons up to the age of 55 years.

Pediatrics

Menactra® is not approved for use in infants below 9 months of age.

ADVERSE REACTIONS

Clinical Trial Adverse Reactions

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 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.

Infants and Toddlers

The safety of Menactra® in infants and toddlers was evaluated in 3569 participants in the US, in 4 clinical trials. Of these, 808 subjects received a second dose of Menactra® alone at 12 to 15 months of age and 2455 subjects received a second dose of Menactra® concomitantly with routinely recommended pediatric vaccines at 12 months. A total of 797 subjects in the control

groups received two or more routinely recommended pediatric vaccines at 12 months of age. Safety was evaluated within 7 days, 30 days and 6 months after vaccination.

Two doses of Menactra® were well tolerated in infants and toddlers. The percentages of subjects with solicited injection site reactions or systemic reactions did not increase after the second dose of Menactra® given alone. The most frequently reported solicited injection site and systemic reactions were injection site tenderness and irritability. The majority of these reactions were of Grade 1 or Grade 2 intensity (see Table 1).

In toddlers who received Menactra® and concomitant pediatric vaccines at 12 months of age, similar frequencies of tenderness, redness and swelling at the Menactra® vaccine injection site and at the concomitant vaccine injection sites were reported. Tenderness was the most frequent solicited injection site reaction and irritability was the most frequent solicited systemic reaction.

Table 1: Frequency of Solicited Reactions Reported in Infants and Toddlers Within 7 Days After Menactra® Vaccination at 9 Months and a Second Dose at 12 Months of Age (5)

		MTA44		MTA37	
		9 months N=407	12 months N=386	9 months N=257	12 months N=246
Subjects with:	**Intensity**	**%**	**%**	**%**	**%**
Injection Site Reactions:					
Tenderness	**Any***	31.7	35.8	35.3	34.2
	Grade 3†	0.5	0.3	0.0	0.4
Erythema	**Any**	22.2	23.0	22.5	23.7
	Grade 3‡	0.5	0.8	2.1	2.6
Swelling	**Any**	11.4	9.8	12.9	13.2
	Grade 3§	0.0	0.5	1.3	1.3
Systemic Reactions:					
Fever Any Route	**Any**	12.9	15.8	9.9	10.1
	Grade 3§	0.8	0.8	0.4	0.4
Vomiting	**Any**	16.1	7.4	17.4	6.6
	Grade 3**	0.5	1.1	1.2	0.4
Crying Abnormal	**Any**	33.9	35.4	37.2	21.5
	Grade 3††	1.8	2.2	3.3	1.3
Drowsiness	**Any**	30.7	28.3	33.1	25.4
	Grade 3‡‡	0.8	0.5	0.8	0.0
Appetite Lost	**Any**	25.1	26.4	25.6	23.7
	Grade 3§§	1.3	2.2	1.2	1.3
Irritability	**Any**	55.3	51.9	55.8	43.0
	Grade 3***	1.6	2.5	4.5	3.9

* Any denotes the proportion of participants reporting a reaction regardless of severity.

† Grade 3: cries when injected limb is moved or the movement of the injected limb is reduced.

‡ Grade 3: ≥ 2.0 inches.

§ Grade 3: > 39.5°C.

** Grade 3: ≥ 6 episodes per 24 hours or requiring parenteral hydration

†† Grade 3: > 3 hours.

‡‡ Grade 3: Sleeping most of the time or difficult to wake up.

§§ Grade 3: Refuses ≥ 3 feeds/meals or refuses most feeds/meals.

*** Grade 3: Inconsolable.

Children 2 to 10 Years Old

The safety of Menactra® in children 2 to 10 years of age was evaluated in 3 clinical trials that enrolled over 2400 participants who received Menactra® and over 2,200 participants who received Menomune®-A/C/Y/W-135. Safety was evaluated within the first 7 days, 28 days and 6 months after vaccination.

Menactra® was well tolerated among children. The majority of the solicited injection site and systemic reactions reported within 7 days after vaccination were mild, with a mean duration of no more than 3 days for the injection site reactions and less than 4 days for the systemic reactions. The most commonly reported solicited adverse reaction was pain at the injection site (40 to 48% of the participants). (See Table 2.)

In children 2 to 4 years of age, previously immunized with a monovalent meningococcal C conjugate vaccine, Menactra® was shown to be well tolerated and had a safety profile comparable to another polysaccharide protein conjugated vaccine [Hib (PRP/T)] used as a control (Trial MTA15). (5) (6)

Table 2: Percentage of Menactra® and Menomune®-A/C/Y/W-135 Recipients Reporting at Least One Solicited Injection Site and/or Systemic Reaction Within 7 Days, by Reaction Type in Children 2 to 10 Years Old, by Study (5)

Event	Study 603-02 Menactra® N = 692		Study 603-02 Menomune®-A/C/Y/W-135 N = 692		Study MTA08 Menactra® N = 1,704		Study MTA08 Menomune®-A/C/Y/W-135 N = 1,515	
	Any*	Severe†	Any	Severe	Any	Severe	Any	Severe
Injection Site Reactions								
Pain	48.1	0.7	46.9	0.3	39.7	0.2	30.4	0.0
Redness	29.5	4.3	30.4	0.4	17.9	2.8	9.4	0.0
Induration	22.1	1.0	15.6	0.1	16.1	0.9	5.2	0.0
Swelling	20.5	1.2	14.6	0.3	14.3	1.3	4.9	0.0
Systemic Reactions								
Irritability‡	35.2	2.7	30.1	0.6	11.0	0.2	12.1	0.4
Drowsiness‡	26.0	1.6	24.1	1.1	10.4	0.2	10.9	0.3
Anorexia§	22.7	1.7	20.3	0.4	8.3	0.3	9.2	0.7
Diarrhea**	15.9	1.6	15.7	0.4	12.1	0.2	13.0	0.3
Fever††	11.4	0.9	12.0	0.6	5.9	0.2	6.0	0.3
Vomiting‡‡	5.9	0.7	7.0	1.1	3.5	0.2	3.1	0.4
Hives§§	1.2	-	0.4	-	-	-	-	-
Arthralgia‡	-	-	-	-	7.3	0.1	7.6	0.0
Rash§§	-	-	-	-	4.1	-	3.5	-
Seizures§§	-	-	-	-	0.0	-	0.0	-

* Any denotes the proportion of participants reporting any reaction regardless of the severity.

† Severe injection site reaction denotes swelling, redness or induration ≥2.0 inches in diameter or pain resulting in unwillingness to move the affected arm.

‡ Severe: requiring bed rest.

§ Severe: skipped ≥3 meals.

** Severe: ≥5 episodes.

†† Severe: ≥39.5°C.

‡‡ Severe: ≥3 episodes.

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

Adolescents and Adults (11 to 55 Years Old)

The safety of Menactra® was evaluated in 6 clinical studies that enrolled 7,640 participants 11 to 55 years old who received Menactra® and 3,041 participants who received Menomune®-A/C/Y/W-135.

Menactra® was well tolerated among adolescents and adults (Table 3). The most commonly reported injection site adverse reactions were pain, induration, redness and swelling. The most common systemic adverse reactions were headache, fatigue and malaise. The majority of injection site and systemic reactions following Menactra® were reported as mild in intensity. Except for redness in adults, injection site reactions were more frequently reported after Menactra® than after Menomune®-A/C/Y/W-135. The majority of injection site and systemic reactions following Menactra® or Menomune®-A/C/Y/W-135 were reported as mild in intensity. No important differences in rates of malaise, diarrhea, anorexia, vomiting, or rash were observed between the vaccine groups. (see Table 3)

Table 3: Percentage of Menactra® and Menomune®-A/C/Y/W-135 Subjects from Comparative Trials Reporting at Least One Solicited Injection Site and/or Systemic Reaction within 7 Days, by Reaction Type in Adolescents (11 to 17) and Adults (18 to 55) (5)

Event	Menactra® Adolescents N = 2,702*		Menomune®-A/C/Y/W-135 Adolescents N = 1,411*		Menactra® Adults N = 2,824†		Menomune®-A/C/Y/W-135 Adults N = 1,613†	
	Any‡	Severe§	Any	Severe	Any	Severe	Any	Severe
Injection Site Reactions								
Pain	64.0	0.2	29.4	0	52.2	0.1	33.9	0
Induration	18.0	0.5	6.4	0	16.6	0.6	8.2	0
Redness	11.5	0.4	6.0	0	13.5	0.8	12.9	0
Swelling	12.6	0.6	4.5	0	11.7	0.7	6.1	0
Systemic Reactions								
Headache**	37.1	1.1	32.5	0.9	40.7	0.8	39.5	1.0
Fatigue**	29.9	1.1	24.6	0.4	34.0	0.7	30.2	0.7
Malaise**	21.9	1.1	16.8	0.4	22.9	0.8	21.0	1.1
Arthralgia**	17.4	0.4	10.2	0.1	19.5	0.4	15.0	0.2
Diarrhea††	11.8	0.3	11.4	0.1	16.6	0.4	14.4	0.4
Anorexia‡‡	11.0	0.4	9.1	0.4	11.6	0.3	9.3	0.4
Chills§§	7.0	0.2	3.5	0.1	8.4	0.3	5.0	0.1
Fever***	4.8	0	2.8	0.1	1.2	0	0.5	0
Vomiting§§	2.0	0.3	1.6	0.3	2.0	0.1	1.4	0.3
Rash†††	1.6	-	1.5	-	1.4	-	1.2	-
Seizures†††	0	-	0	-	0	-	0	-

* Includes all subjects who provided data from comparative trials MTA02 and MTA04.

† Includes all subjects who provided data from comparative trials MTA09 and MTA14.

‡ Any denotes the proportion of participants reporting any reaction regardless of the severity.

§ Severe injection site reaction denotes swelling, redness or induration ≥2.0 inches in diameter or pain resulting in unwillingness to move the affected arm.

** Severe: requiring bed rest.

†† Severe: ≥5 episodes.

‡‡ Severe: skipped ≥3 meals.

§§ Severe: ≥3 episodes.

*** Severe: ≥39.5°C.

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

Data from Post-Marketing Experience

The following additional adverse events have been spontaneously reported during the post-marketing use of Menactra®. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Immune system disorders:

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

Nervous system disorders:

Guillain-Barré syndrome (see WARNINGS AND PRECAUTIONS), paraesthesia, vasovagal syncope, dizziness, convulsion, facial palsy, acute disseminated encephalomyelitis, transverse myelitis.

Hematologic disorders:

Thrombocytopenia.

Musculoskeletal and connective tissue disorders:

Myalgia.

Physicians, nurses and pharmacists should report any adverse occurrences temporally associated with the administration of the product in accordance with local requirements and to the Global Pharmacovigilance and Epidemiology Department, Sanofi Pasteur Limited, 1755 Steeles Avenue West, Toronto, ON, M2R 3T4, Canada. 1-888-621-1146 (phone) or 416-667-2435 (fax).

Post-Marketing Safety Study

The risk of GBS following receipt of Menactra® 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®. Of 72 medical chart-confirmed GBS cases, none had received Menactra® 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.

DRUG INTERACTIONS

Vaccine Drug Interactions

Immunosuppressive treatments may interfere with the development of the expected immune response. (See WARNINGS AND PRECAUTIONS.)

Concomitant Vaccine Administration

Menactra® and MMRV, MMR+V, PCV, Hep A or Hib vaccines when administered concomitantly or separately at 12 months of age, had similar safety profiles. The immunogenicity profiles of Menactra® and MMRV, MMR+V, or Hib vaccines were also similar when these vaccines were given concomitantly or separately. When PCV was administered concomitantly with Menactra®, antibody responses to pneumococcal antigens were non-inferior to the responses to concomitant administration of PCV and MMRV for four of the seven PCV serotypes. PCV elicited a strong immune response to all seven serotypes as evidenced by high and consistent pneumococcal opsonophagocytic assay (OPA) GMTs and ELISA GMCs in both groups.

No data are available on Menactra® and DTaP containing vaccines administered concomitantly in the second year of life.

The concomitant administration of Menactra® with tetanus and reduced-dose diphtheria vaccine (Td) to adolescents revealed no apparent increase in reported adverse events or specific safety concern related to the diphtheria toxoid carrier protein content. The anti-diphtheria response was much higher after concomitant administration of Td with Menactra® compared to the administration of Td followed by Menactra® 28 days later.

The concomitant administration of Menactra® and Typhim Vi® (*Salmonella typhi* Vi Capsular Polysaccharide Vaccine) was well tolerated in adults, 18 to 55 years old. The immune response to the two vaccines was comparable when Menactra® and Typhim Vi® were given concurrently or separately, 28 days apart.

Vaccines administered simultaneously should be given using separate syringes at separate sites. Menactra® should not be mixed in the same syringe with other parenterals.

DOSAGE AND ADMINISTRATION

Recommended Dose

In infants or toddlers, 9 months through 23 months of age, 2 single doses (0.5 mL) of Menactra® should be administered at least 3 months apart. In persons 2 through 55 years of age, a single dose of Menactra® should be administered. Menactra® should be injected by the intramuscular route.

The need for, or timing of, the administration of a booster has not yet been determined.

Administration

Inspect for extraneous particulate matter and/or discolouration before use. (See DESCRIPTION.) If these conditions exist, the product should not be administered.

Shake the vaccine well until a uniform, clear to slightly turbid liquid results. Cleanse the vial stopper with a suitable germicide prior to withdrawing the dose. Do not remove either the stopper or the metal seal holding it in place. Aseptic technique must be used. Use a separate sterile needle and syringe, or a sterile disposable unit for each individual recipient, to prevent disease

transmission. Needles should not be recapped and should be disposed of according to biohazard waste guidelines. (See WARNINGS AND PRECAUTIONS.)

For information on vaccine administration see the current edition of the Canadian Immunization Guide or visit the Health Canada website.

Administer the total volume of 0.5 mL **intramuscularly** (IM). For infants younger than 1 year, the preferred site is the anterolateral aspect of the thigh; for children, adolescents and adults it is the deltoid muscle.

Give the patient a permanent personal immunization record. In addition, it is essential that the physician or nurse record the immunization history in the permanent medical record of each patient. This permanent office record should contain the name of the vaccine, date given, dose, manufacturer and lot number.

Overdosage

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

Mechanism of Action

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

Duration of Effect

A group of 2 to 3 year old children (N = 92) followed for up to 3 years after a single dose of Menactra® had 1.7 to 5.2 fold higher bactericidal antibody levels than an age-matched vaccine naïve control group. The duration of protection against invasive meningococcal disease remains unknown.

STORAGE AND STABILITY

Store at 2° to 8°C (35° to 46°F). **Do not freeze.** Discard product if exposed to freezing.

Do not use after the expiration date.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

The stopper of the vial presentation of this vaccine does not contain latex (natural rubber).

1 x 1 Dose Vial

5 x 1 Dose Vial

Composition

Menactra® is a clear to slightly turbid liquid.

Each single dose (0.5 mL) is formulated to contain:

Active Ingredients

4 µg each of meningococcal A, C, Y and W-135 polysaccharides conjugated to a total of approximately 48 µg of a diphtheria toxoid protein carrier

Sodium Chloride	4.25 mg
Sodium Phosphate, Dibasic, Anhydrous	QS phosphate 10 mM
Sodium Phosphate, Monobasic	QS phosphate 10 mM

Other Ingredients

Water for Injection	QS 0.5 mL

Menactra® is preservative-free. No adjuvant is added.

Vaccine Information Service: 1-888-621-1146 or 416-667-2779. Business hours: 8 a.m. to 5 p.m. Eastern Time, Monday to Friday.

Full product monograph available on request or visit us at www.sanofipasteur.ca

Product information as of June 2012.

Manufactured by:
Sanofi Pasteur Inc.
Swiftwater, PA, 18370 USA

Distributed by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

R5-0612 Canada

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

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

Product Characteristics

Menactra® is a sterile, clear to slightly turbid liquid of *Neisseria meningitidis* serogroups A, C, Y and W-135 capsular polysaccharide antigens individually conjugated to diphtheria toxoid protein. The 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.

N. meningitidis is cultured on Mueller Hinton agar (8) and Watson Scherp (9) media. The purified polysaccharide is extracted from the *N. meningitidis* cells and separated from the media by procedures that include centrifugation, detergent precipitation, alcohol precipitation, solvent extraction and diafiltration. The diphtheria toxoid protein is purified from cultures of *Corynebacterium diphtheriae* and formalin-detoxified. No preservative or adjuvant is added during manufacture. Potency of Menactra® is determined for each lot by the amount of polysaccharide that is conjugated to diphtheria toxoid protein in each dose.

CLINICAL TRIALS

Study Demographics and Trial Design

The data supporting safety and immunogenicity of Menactra® was gathered from 14 controlled clinical trials summarized in Table 4. The age, sex and ethnic distribution was similar between the Menactra® and the control groups.

Table 4: Summary of Clinical Studies Supporting the Safety and Immunogenicity of Menactra®

Trial	Trial Type (Safety and Immunogenicity)	Mean Age (Years)	Total Enrolled	Number Receiving Menactra®	Male /Female
MTA09	Comparison versus Menomune®-A/C/Y/W-135 in 18 to 55 year-olds	29	2,554	1,384	971/1,583
MTA14	Lot Consistency and Comparison* versus Menomune®-A/C/Y/W-135 in 18 to 55 year-olds	34.5	2,040	1,582	722/1,318
MTA11	Concomitant Administration with Typhim Vi® in 18 to 55 year-olds	32.6	945	945	301/644
MTA02	Comparison versus Menomune®-A/C/Y/W-135 in 11 to 18 year-olds	14.3	881	440	486/395
MTA04	Comparison versus Menomune®-A/C/Y/W-135 in 11 to 18 year-olds*	15.5	3,242	2,270	1,651/1,591
MTA12	Concomitant Administration with Tetanus and Diphtheria Combined Vaccine in 11 to 17 year-olds	12.9	1,019	1,019	520/499
603-02 (Study A)	Comparison versus Menomune®-A/C/Y/W-135 in 2 to 10 year-olds	3.6	1,398	696	731/667
MTA08 (Study B)	Comparison versus Menomune®-A/C/Y/W-135 in 2 to 10 year-olds	5.9	3,231	1,712	1,632/1,599
MTA15	Comparison versus Hib (PRP/T) vaccine in monovalent meningococcal C conjugate vaccinated subjects in 2 to 4 year-olds	37.3 (months)	102	52	53/49
MTA17	Menactra®-induced immune memory evaluation in 2 to 3 year-olds†	4.2	171	N/A	85/86
MTA26	Evaluation of 1 or 2 doses of Menactra® between 9 and 18 months of age	18.7 (months)	378	302	199/179
MTA44	Evaluation of 2 doses of Menactra® at 9 and 12 months of age and concomitant administration of MMRV or PCV at 12 months of age	279.3 (days)	1128	1118	551/567

Trial	Trial Type (Safety and Immunogenicity)	Mean Age (Years)	Total Enrolled	Number Receiving Menactra®	Male /Female
MTA37	Evaluation of 2 doses of Menactra® at 9 and 12 months of age and non-interference with concomitant MMRV (or MMR+V) or PCV at 12 months of age	309.7 (days)	1664	1167	835/829
MTA48	Evaluation of 2 doses of Menactra® at 9 and 12 months of age and concomitant administration of MMRV (or MMR+V), PCV, HepA at 12 months of age*	328.2 (days)	1378	1053	706/672

* safety only

† immunogenicity only

Summary of Immunogenicity Studies

Assessment of Immunogenicity

The presence of bactericidal anti-capsular meningococcal antibodies has been associated with protection from invasive meningococcal disease. Menactra® induces the production of bactericidal antibodies specific to the capsular polysaccharides of serogroups A, C,Y and W-135. Serum bactericidal antibody (SBA) was established as a serological correlate of protection for group C meningococcal infection in studies in military recruits undertaken in the 1960s. These studies showed that those with naturally acquired SBA titres ≥1:4 measured using human complement (SBA-HC) were protected from meningitis caused by *Neisseria meningitidis* serogroup C. (7) An alternative complement source for the SBA is 3 to 4-week-old baby rabbit serum (SBA-BR). (10) While a group C SBA-BR titre ≥1:128 predicts protection against meningococcal serogroup C disease, it has been shown to underestimate vaccine efficacy; moreover, the cut off ≥1:8 was found to be the most consistent correlate with the observed efficacy of Meningococcal group C conjugate vaccine in the UK. (10) A serologic correlate that predicts clinical protection has not been established for serogroups A, Y and W-135

The response to vaccination following two doses of vaccine administered to infants and toddlers 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 titer 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. (11) For individuals 2 through 55 years of age, vaccine efficacy was inferred from the demonstration of immunologic equivalence to a licensed meningococcal polysaccharide vaccine, Menomune–A/C/Y/W-135 vaccine as assessed by Serum Bactericidal Assay (SBA).

Immunogenicity in Infants and Toddlers

In a randomized, multi-center trial, infants received Menactra® vaccine at 9 months and 12 months of age (MTA44). The first Menactra® dose was administered alone, followed by a second Menactra® dose given alone (N=404), or with MMRV vaccine (N=302), or with PCV (N=422). For all participants, sera were obtained approximately 30 days after last vaccination.

The majority of subjects (>90% of subjects in each study group for serogroups A, C, and Y, and >80% for serogroup W-135) achieved SBA-H titers ≥ 8, 30 days after the second dose of Menactra® at 12 months of age (see Table 5).

Table 5: Antibody Responses in Toddlers Receiving the Second dose of Menactra® at 12 Months With or Without Concomitant Vaccines (5)

Evaluation Criterion	Serogroup	MTA44		
		Menactra® (N=277)	Menactra® + MMRV (N=180)	Menactra® + PCV (N=269)
% of subjects with titer ≥ 8	A	95.6	92.7	90.5
	C	100.0	98.9	97.8
	Y	96.4	96.6	95.1
	W-135	86.4	88.2	81.2
GMT	A	54.9	52.0	41.0
	C	141.8	161.9	109.5
	Y	52.4	60.2	39.9
	W-135	24.3	27.9	17.9

Administration of Menactra® to toddlers at 12 months and 15 months of age (N=65) was evaluated in a US study (Table 4, MTA26). Prior to the first dose, 33.3% of participants had an SBA-HC titer ≥1:8 to serogroup A, and 0-2% to serogroups C, Y and W135. After the second dose, percentages of participants with an SBA-HC titer >1:8 were: 85.2%, serogroup A; 100.0%, serogroup C; 96.3%, serogroup Y; 96.2%, serogroup W-135.

In the same study, a group of toddlers received Menactra® at 9 months and 15 months of age (N=65). Prior to the first dose 43.9% of participants had an SBA-HC titer ≥1:8 to serogroup A, and 0-2.2% to serogroups C, Y and W-135. After the second dose, percentages of participants with an SBA-HC titer >1:8 were: 89.4%, serogroup A; 100.0%, serogroup C; 94.0%, serogroup Y; 92.0%, serogroup W-135.

Concomitant MMRV (or MMR+V), MMRV+Hib, or PCV Vaccinations

In the active-controlled trial (MTA37), 1167 infants received Menactra® at 9 months. At 12 months, Menactra® was administered alone (N=246) or concomitantly with MMRV (N=616), MMR + V (N=48) or PCV (N=230). A control group received only MMRV + PCV (N=476) at 12 months of age. Sera were obtained approximately 30 days after the last vaccinations. Measles, mumps, rubella and varicella antibody responses among toddlers who received Menactra® and MMRV (or MMR + V) were comparable to corresponding antibody responses among toddlers who received MMRV and PCV.

In a subgroup of subjects that received Hib vaccine concomitantly with Menactra® and MMRV at 12 months of age, 100% of subjects achieved anti-PRP antibody concentrations ≥ 1 µg/mL approximately 30 days after vaccination.

When Menactra® was given concomitantly with PCV, 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 (OPA) GMT data were consistent with IgG GMC data. At least 99% of subjects achieved OPA anti-pneumococcal antibody titers ≥8, and ≥ 97% of the subjects achieved OPA titers ≥ 72.

Immunogenicity in Children 2 to 10 years of Age

Immunogenicity in Meningococcal Vaccine-Naïve Children 2 to 10 Years of Age

Results from the comparative clinical trial conducted in 1,398 children 2 to 10 years old showed that the immune responses to Menactra® was not inferior to those observed in the Menomune®-A/C/Y/W-135 group for each of the four serogroups. The Geometric Mean Titres (GMTs) at 28 days and six months after immunization were higher in children who received Menactra® than those who received Menomune®-A/C/Y/W-135. (See Table 6.) For all vaccine serogroups 86.2 to 98.6% of children with undetectable SBA titre (<8) at baseline, seroconverted to achieve a ≥4-fold rise in Day 28 SBA titres. SBA titre levels of ≥1:128 were achieved in 81.5% for serogroup C to 96.9% for serogroup A. Seroprotection rates (SBA titre ≥1:8) observed at Day 28 were 99.5, 96.2, 98.3 and 96.5%, for serogroups A, C, Y and W-135, respectively.

Table 6: Antibody Responses in Children 2 to 10 Years Old in Trial 603-02 (5)

Immune Response Criteria	% Seroconversion (Day 0 titre <1:8 and Day 28 titre ≥1:32)		% ≥4-fold Rise		% with Day 28 titre ≥1:8		GMT on Day 28		GMT at 6 Months	
Serogroup	**Menactra® N = 696**	**Menomune®-A/C/Y/W-135 N = 702**	**Menactra® N = 696**	**Menomune®-A/C/Y/W-135 N = 702**	**Menactra® N = 696**	**Menomune®-A/C/Y/W-135 N = 702**	**Menactra® N = 696**	**Menomune®-A/C/Y/W-135 N = 702**	**Menactra® N = 696**	**Menomune®-A/C/Y/W-135 N = 702**
A	98.6 (N = 275/279)	94.7 (N = 265/280)	87.7	83.8	99.5	98.3	1,700	893	1,054	216
C	87.9 (N = 297/338)	80.1 (N = 293/366)	73.4	68.9	96.2	89.4	354	231	137	66
Y	86.2 (N = 75/87)	75.0 (N = 72/96)	56.6	45.6	98.3	97.6	637	408	592	240
W-135	96.0 (N = 384/400)	89.6 (N = 359/401)	91.0	85.4	96.5	93.4	750	426	362	137

Immunogenicity in Children 2 to 10 Years Old with Prior Vaccination with a Monovalent Meningococcal C Conjugate Vaccine

The capacity of Menactra® to induce a booster response to serogroup C capsular polysaccharide and to prime for serogroups A, Y and W-135 capsular polysaccharides was documented by vaccinating children 2 to 4 years old immunized with monovalent meningococcal C conjugate vaccine >1 year earlier. (See Table 4, Trial MTA15.)

For all vaccine serogroups, 79.6 to 97.7% of children achieved a ≥4-fold rise in Day 28 SBA titres. In particular, 93.2% of children developed a ≥4-fold rise against serogroup C. With the exception of one recipient for serogroup Y, all Menactra® recipients in this trial achieved a titre of 1:128 against all serogroups (Table 7).

This study suggests that Menactra® can be used to boost the serogroup C antibody responses in subjects primed with a monovalent meningococcal C conjugate vaccine and as a result, is not associated with the hyporesponsiveness observed following meningococcal polysaccharide vaccines.

Table 7: SBA Responses in Children 2 to 4 years old with Prior Vaccination with a Monovalent Meningococcal C Conjugate Vaccine in Trial MTA15 (5)

Immune Response Criteria	% ≥4-fold Rise		% with Day 28 titre ≥1:8		% with Day 28 titre ≥1:128		GMT on Day 28	
Serogroup	**Menactra® N = 44**	**Hib N = 36**	**Menactra® N = 44**	**Hib N = 36**	**Menactra® N = 44**	**Hib N = 36**	**Menactra® N = 44**	**Hib N = 36**
A	97.7	30.6	100	77.8	100	77.8	11,404	199
C	93.2	5.6	100	44.4	100	30.6	12,535	23
Y	79.6	2.8	100	88.9	98	83.3	4,032	299
W-135	97.7	22.2	100	58.3	100	36.1	5,978	32

Immune Memory in Children 2 to 3 Years Old

A sub-group of ninety-two (92) two to three year old subjects who participated in Trial 603-02 were recruited approximately 2 to 3 years later to evaluate persistence of bactericidal antibody and immune memory. An age matched vaccine naïve control group was also recruited. Each group received a reduced dose (1/10th the dose of Menomune®-A/C/Y/W-135) of polysaccharide vaccine. Prior to challenge with polysaccharide vaccine, subjects primed with Menactra® showed higher levels of bactericidal antibody than the age matched vaccine naïve control group, for all serogroups. Using a non-standard modified ELISA assay, Menactra®-primed subjects showed higher avidity indices than those measured in the control group. After challenge with the reduced dose of polysaccharide vaccine, subjects primed with Menactra® (PM Group; N = 46) showed GMT's that were higher than those seen in the control group (N = 26). Despite some study limitations, these observations are consistent with the induction of immune memory in young children. It is noted, however, that compared to baseline, the fold increase in bactericidal

antibody levels after the reduced dose polysaccharide vaccine, was significant in both the Menactra®-primed and the control groups.

Immunogenicity in Adolescents 11 to 18 Years Old

Results from the comparative clinical trial conducted in 881 adolescents 11 to 18 years old showed that the immune responses to Menactra® and Menomune®-A/C/Y/W-135 were similar for all four serogroups. (See Table 8.) For all vaccine serogroups 98.2 to 100% of adolescents with undetectable SBA titre (<8) at baseline seroconverted to achieve a ≥4-fold rise in Day 28 SBA titres. Furthermore 98.6 to 99.8% achieved antibody titre levels of 1:128 against the four serogroups. Seroprotection rates (SBA titre ≥1:8) observed at Day 28 were 100, 99.8, 100 and 99.1% for serogroups A, C, Y and W-135, respectively.

Table 8: SBA Responses in Adolescents 11 to 18 Years Old in Trial MTA02 (5)

Immune Response Criteria	% Seroconversion (Day 0 titre <1:8 and Day 28 ≥1:32)		% ≥4-fold Rise		GMT on Day 28	
Serogroup	**Menactra® N = 423**	**Menomune®-A/C/Y/W-135 N = 423**	**Menactra® N = 423**	**Menomune®-A/C/Y/W-135 N = 423**	**Menactra® N = 423**	**Menomune®-A/C/Y/W-135 N = 423**
A	100 (N = 81/81)	100 (N = 93/93)	92.7	92.4	5,483	3,246
C	98.7 (N = 153/155)	99.3 (N = 151/152)	91.7	88.7	1,924	1,639
Y	98.4 (N = 60/61)	100 (N = 47/47)	81.8	80.1	1,322	1,228
W-135	98.2 (N = 161/164)	99.3 (N = 138/139)	96.7	95.3	1,407	1,545

Concomitant Td Vaccination in Adolescents

The concomitant use of Menactra® and Td was evaluated in a double-blind, randomized, controlled clinical trial conducted in 1,021 participants 11 to 17 years old. One group received Td and Menactra® (at separate injection sites) at Day 0 and a saline placebo 28 days later. The other group received Td and a saline placebo at Day 0 and Menactra® 28 days later. Sera were obtained approximately 28 days after each respective vaccination. As shown in Table 9, 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® was given concomitantly with Td than when Menactra® was given one month following Td. Participants in this trial also achieved a much higher anti-diphtheria response when Td and Menactra® were administered concomitantly compared to separate administration with no significant change in adverse events. The clinical relevance of this finding has not been fully evaluated. No interference was observed in the immune response to the tetanus component following either concomitant or sequential vaccination.

Table 9: Comparison of Antibody Responses for Td and Menactra® for Participants 11 to 17 Years Old on Day 28 Following Respective Vaccinations in Trial MTA12 (5)

		Td* + Menactra®† at Day 0 Placebo at Day 28		Td + Placebo at Day 0 Menactra® at Day 28	
Antigen		**N‡**		**N‡**	
Tetanus	% >0.1 IU/mL§	464	100	477	100
	GMT	464	11.5	477	13.6
Diphtheria	%>0.1 IU/mL**	465	100	473	100
	GMT	465	120.9	473	8.4
Serogroup A	GMT	466	1,131.3	478	10,391
	% ≥4-fold rise††	465	90.1	478	90.6
Serogroup C	GMT	466	5,059	478	2,136
	% ≥4-fold rise	465	91.2	478	82.4
Serogroup Y	GMT	466	3,391	478	1,331
	% ≥4-fold rise	465	85.8	478	65.1
Serogroup W-135	GMT	466	4,195	478	1,339
	% ≥4-fold rise	465	96.3	478	87.7

* Response to Td assessed as follows: Tetanus ELISA and Diphtheria MIT (Micrometabolic Inhibition Test) (IU/mL).

† Response to MENACTRA® 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).

§ A serum tetanus antitoxin level of at least 0.01 IU/mL is considered the minimum protective level.

** 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.

†† MENACTRA® when given concomitantly with Td was non-inferior to MENACTRA® 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 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.

Immunogenicity in Adults 18 to 55 Years Old

Results from the comparative clinical trial conducted in 2,554 adults 18 to 55 years old showed that the immune responses to Menactra® and Menomune®-A/C/Y/W-135 were similar for all four serogroups. (See Table 10.) For all vaccine serogroups 90.7 to 100% of participants with undetectable SBA titre (<8) at baseline seroconverted to achieve a ≥4-fold rise in Day 28 SBA titres. Furthermore 97 to 99.8% achieved antibody titre levels of 1:128 against the four serogroups. Seroprotection rates (SBA titre ≥1:8) observed at Day 28 were 100, 99.8, 98.4 and 99.3% for serogroups A,C,Y and W-135, respectively.

Table 10: SBA Responses in Adults 18 to 55 Years Old in Trial MTA09 (5)

Immune Response Criteria	% Seroconversion (Day 0 titre <1:8 and Day 28 titre ≥1:32)		% ≥4-fold Rise		GMT on Day 28	
Serogroup	**Menactra® N = 1,280**	**Menomune®-A/C/Y/W-135 N = 1,098**	**Menactra® N = 1,280**	**Menomune®-A/C/Y/W-135 N = 1,098**	**Menactra® N = 1,280**	**Menomune®-A/C/Y/W-135 N = 1,098**
A	100 (N = 156/156)	99.3 (N = 143/144)	80.5	84.6	3,897	4,114
C	99.4 (N = 343/345)	97.7 (N = 297/304)	88.5	89.7	3,231	3,469
Y	90.7 (N = 253/279)	96.9 (N = 221/228)	73.5	79.4	1,750	2,449
W-135	96.5 (N = 360/375)	99.1 (N = 325/328)	89.4	94.4	1,271	1,871

Concomitant Salmonella typhi Vi Capsular Polysaccharide Vaccination, (Typhim Vi®) in Adults

The concomitant use of Menactra® and Typhim Vi® (recommended for certain travellers) was evaluated in a double-blind, randomized, controlled clinical trial conducted in 945 participants 18 to 55 years old. One group received Typhim Vi® and Menactra® (at separate injection sites) at Day 0 and a saline placebo 28 days later. The other group received Typhim Vi® and a saline placebo at Day 0 and Menactra® 28 days later. Sera were obtained approximately 28 days after each respective vaccination. The immune responses to Menactra® and to Typhim Vi® when given concurrently were comparable to the immune response when Menactra® or Typhim Vi® was given alone.

Kinetics of the Immune Response

There are no data on the kinetics of the response with Menactra®.

Duration of Protection

A group of 2 to 3 year old children (N = 92), were followed for 2 to 3 years after a single dose of Menactra®. These participants had 1.7- to 5.2-fold higher bactericidal antibody levels than an age-matched vaccine naïve control group. Conjugation of the capsular polysaccharide antigens to the diphtheria protein converts a T-cell independent response to one that is T-cell dependent. However, the duration of protection against invasive meningococcal disease remains unknown. A subgroup of these subjects was challenged with a reduced dose of meningococcal polysaccharide vaccine. The bactericidal antibody levels on Day 28 post-challenge were higher in the Menactra®-primed subjects (N = 46) than the control group (N = 26). This antibody response is consistent with immune memory. It is noted, however, that compared to baseline, the fold increase in bactericidal antibody levels after the reduced dose polysaccharide vaccine, was significant in both the Menactra®-primed and the control groups.

Clinical Trial Adverse Drug Reactions

Clinical trials are conducted under very specific conditions, therefore, the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Summary of Safety Studies

The safety of Menactra® was evaluated in 3569 infants and toddlers in the US in 4 clinical trials. Of these, 808 subjects received a second dose of Menactra® alone at 12 to 15 months of age and 2455 subjects received a second dose of Menactra® concomitantly with routinely recommended pediatric vaccines at 12 months. A total of 797 subjects in the control groups received two or more routinely recommended pediatric vaccines at 12 months of age.

The safety of Menactra® was evaluated in 9 clinical studies that enrolled 10,100 participants 2 to 55 years old who received Menactra® and 5,262 participants who received Menomune®-A/C/Y/W-135. There were no substantive differences in demographic characteristics between the vaccine groups. Among Menactra® recipients 2 to 55 years of age, 24.4, 36.9 and 38.7% were in the 2-10, 11-18 and 18-55 -year age groups, respectively. Among Menomune®-A/C/Y/W-135 recipients 2 to 55 years of age, 42.2, 26.8 and 30.9% were in the 2-10, 11-18 and 18-55-year age groups, respectively.

Solicited injection site and systemic reactions were monitored daily for 7 days post-vaccination using a diary card. Participants were monitored for 28 days (30 days for infants and toddlers) 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.

Safety Summary in Infants and Toddlers

Three Phase 3 trials (MTA44, MTA37 and MTA 48) evaluated the safety of Menactra® in 3267 subjects where the second dose of Menactra was administered either alone or concomitantly with licensed vaccines at 12 months of age. The percentage of subjects with any solicited injection site reactions at the Menactra® injection site was comparable across the study groups: 41% to 52% after the first dose of Menactra® at 9 months and 43% to 58% after second dose of Menactra at 12 months administered alone or with concomitant licensed vaccines. At any of the injection sites, the most common solicited reaction was tenderness.

Solicited systemic reactions were reported in 64 % to 71% of subjects across the study groups after the first dose of Menactra® at 9 months, in 56% to 74% of subjects after second dose of Menactra at 12 months administered alone or with concomitant licensed vaccines, and in 75% to 77% of subjects in control groups that received only licensed vaccines. Irritability was the most common solicited systemic reaction reported after either the 9-month or the 12-month vaccination(s).

Safety Summary in Children 2 to 10 Years Old

The safety profile of Menactra® in children 2 to 10 years of age was evaluated in 3 clinical trials that enrolled over 2,400 children who received Menactra® and over 2,200 children who received Menomune®-A/C/Y/W-135. Two of the studies documented the safety profile of Menactra® in a meningococcal vaccinated naïve population (Table 4, Trials 603-02 and MTA08). The third study documented the safety profile of Menactra® in children previously vaccinated with a monovalent meningococcal C conjugate vaccine (non-naïve population) (Table 4, Trial MTA15). The safety profile of Menactra® is reported separate for these two populations.

The majority of the solicited injection site and systemic reactions reported within 7 days after vaccination were mild, with a mean duration of no more than 3 days for the injection site reactions and less than 4 days for the systemic reactions.

Safety in Meningococcal-vaccine Naïve Population

The most commonly reported solicited adverse reaction was pain at the injection site (40 to 48% of the participants).

Severe injection site and systemic reactions were uncommon. Severe injection site reactions occurred more frequently after Menactra® than after Menomune®-A/C/Y/W-135 in both trials. Severe systemic reactions occurred with similar frequency after Menactra® and Menomune®-A/C/Y/W-135 in Trial MTA08, but they were more frequent after Menactra® than after Menomune®-A/C/Y/W-135 in Trial 603-02 (7.6% of children who received Menactra® compared to 3.6% of children who received Menomune®-A/C/Y/W-135) although this trial was not statistically powered to detect significant differences for these reactions between the two trial groups.

Safety in Children Previously Vaccinated with Meningococcal Group C Conjugate Vaccine

Trial MTA15, performed in the UK, documented the safety profile of Menactra® compared with another PS-protein conjugated vaccine [Hib (PRP/T)] when used in children (mean age 3 years) previously vaccinated with a monovalent meningococcal C conjugate vaccine. The most commonly reported solicited adverse reaction was irritability (reported by 57% of the participants).

No participant vaccinated with Menactra® presented with a probably or definitely related adverse event.

Safety Summary in Participants 11 to 55 Years Old

The safety of Menactra® was evaluated in 6 clinical studies that enrolled 7,640 participants 11 to 55 years old who received Menactra® and 3,041 participants who received Menomune®-A/C/Y/W-135. There were no substantive differences in demographic characteristics between the vaccine groups. Among Menactra® recipients of all ages, 21.3, 53.2 and 25.5% were in the 11 to 14, 15 to 25 and 26 to 55 year age groups, respectively. Among Menomune®-A/C/Y/W-135 recipients of all ages, 16.1, 51.9 and 32.0% were in the 11 to 14, 15 to 25 and 26 to 55 year age groups, respectively.

The most commonly reported solicited adverse reactions were pain at the injection site and headache (respectively 55 and 37% in the whole population).

The two primary safety studies were randomized, active-controlled trials that enrolled participants 11 to 18 years old (Menactra®, N = 2,270; Menomune®-A/C/Y/W-135, N = 972) and 18 to 55 years old (Menactra®, N = 1,384; Menomune®-A/C/Y/W-135, N = 1,170), respectively. At least 94% of participants from the two studies completed the 6-month follow-up evaluation.

Adverse Events in Concomitant Vaccine Studies

Safety with Concomitant Pediatric Vaccines

The study design and number of participants in Trials MTA37, MTA44 and MTA48, are described in Table 4. The frequencies of solicited reactions reported in toddlers that received the second dose of Menactra® concomitantly with routine pediatric vaccines at 12 months of age were comparable to those reported in the control groups administered only routine pediatric vaccines. The most frequently reported solicited injection site and systemic reactions were tenderness and irritability (see Table 11). The majority of solicited injection site and systemic reactions were of Grade 1 or Grade 2 intensity and resolved within 3 days after vaccination.

Table 11: Percentage of Solicited Reactions Reported in Toddlers After the Second Dose of Menactra® With Concomitant Vaccines at 12 months of Age (Trials MTA37, MTA44 and MTA48)

Subjects with:	Intensity	Menactra® (N=632) %	Menactra® + MMRV (N=825) %	Menactra® + PCV (N=621) %	Menactra® + MMRV + PCV + HepA (N=938) %
Injection Site Reactions*:					
Tenderness	**Any**†	35.2	38.1	48.9	48.5
	Grade 3‡	0.3	0.8	1.2	1.3
Erythema	**Any**	23.3	24.2	26.6	30.1
	Grade 3§	1.5	2.6	2.8	0.1
Swelling	**Any**	11.1	13.4	16.1	16.2
	Grade 3§	0.8	1.5	1.2	0.1
Systemic Reactions :					
Fever Any Route	**Any**	13.7	22.4	20.2	24.5
	Grade 3**	0.7	2.7	1.7	1.9
Vomiting	**Any**	7.1	10.4	9.7	11.0
	Grade 3††	0.8	0.6	0.0	0.2
Crying Abnormal	**Any**	30.1	40.2	37.0	40.0
	Grade 3‡‡	1.9	2.3	3.5	2.3
Drowsiness	**Any**	27.2	32.1	33.1	39.8
	Grade 3§§	0.3	0.9	0.8	1.1
Appetite Lost	**Any**	25.4	31.9	29.7	35.7
	Grade 3***	1.9	1.5	2.0	2.2
Irritability	**Any**	48.5	58.7	58.3	62.1
	Grade 3†††	3.0	3.3	4.2	3.5

* Solicited Injection Site Reactions that occurred at the Menactra Injection Site

† Any denotes the proportion of participants reporting a reaction regardless of severity

‡ Grade 3: cries when injected limb is moved or the movement of the injected limb is reduced

§ Grade 3: ≥ 2.0 in

** Grade 3: > 39.5°C

†† Grade 3: ≥ 6 episodes per 24 hours or requiring parenteral hydration

‡‡ Grade 3: > 3 hours

§§ Grade 3: Sleeping most of the time or difficult to wake up

*** Grade 3: Refuses ≥ 3 feeds/meals or refuses most feeds/meals

††† Grade 3: Inconsolable

Safety with Concomitant Td Vaccine

See Table 4 for a description of the study design (Trial MTA12) and number of participants. The two vaccine groups reported similar frequencies of injection site pain, induration, redness and swelling at the Menactra® injection site and Td injection site. Pain was the most frequent injection site 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 injection site 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® was administered 28 days after Td. In both groups, the most common reactions were headache (Menactra® + Td, 36%; Td + Placebo, 34%; Menactra® alone, 22%) and fatigue (Menactra® + Td, 32%; Td + Placebo, 29%; Menactra® alone, 17%). No important differences in rates of malaise, diarrhea, anorexia, vomiting, or rash were observed between the groups. Fever ≥40.0ºC occurred in ≤0.5% in all groups. No seizures occurred in either group.

Safety with Concomitant Typhim Vi® Vaccine

See Table 4 for a description of the study design and number of participants. The two vaccine groups reported similar frequencies of injection site pain, induration, redness and swelling at the Menactra® injection site, as well as at the Typhim Vi® injection site. Pain was the most frequent injection site reaction reported at both the Menactra® and Typhim Vi® injection site. More participants experienced pain after Typhim Vi® vaccination than after Menactra® vaccination (76 versus 47%). The majority (70-77%) of injection site 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®, 41%; Typhim Vi® + Placebo, 42%; Menactra® alone, 33%) and fatigue (Menactra® + Typhim Vi®, 38%; Typhim Vi® + Placebo, 35%; Menactra® 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.

Serious Adverse Events (SAE) in All Safety Studies

In infants and toddlers who received 2 doses of Menactra® alone (at 9 months and 12 months) or the second dose of Menactra® with concomitant routine pediatric vaccines, the percentage of subjects with at least one SAE after each vaccination was 2.0% to 2.5%. In participants who received one or more pediatric vaccines without the co-administration of Menactra® at 12 months of age, SAEs occurred at a rate of 1.6% to 3.6 % depending on the number and type of vaccines received.

During nine clinical safety studies performed in 2 to 55 year-old participants, 1.8% (105/10,100) of participants who received Menactra® and 1.1% (57/5,262) of participants who received Menomune®-A/C/Y/W-135 experienced at least one SAE. The events reported were consistent with events expected in healthy children, adolescent and adult populations. (5)

Non-Clinical Safety Data

Data in animals revealed no unexpected findings and no target organ toxicity. (5)

A toxicological study in rats demonstrated that one or two intramuscular administrations of one human dose per animal did not show toxicity. (5)

Incompatibilities / Compatibilities

This vaccine must not be mixed with other vaccines or medicinal products in the same syringe.

ADDITIONAL RELEVANT INFORMATION

Invasive Meningococcal Disease (IMD) continues to be an important cause of illness, death and long-term disability.

IMD has three main presentations: meningococcemia, meningococcal meningitis and meningococcal pneumonia-with a combined mortality rate of 10%. Death typically occurs within 24-48 hours of onset of symptoms. Of those who survive the disease, 11 to 19% are permanently disabled as a result of neurological sequelae including hearing loss, speech disorders, mental retardation, seizures and paralysis. Disease survivors can also suffer from loss of limbs, lung damage and psychological disorders. Meningococcemia is the most aggressive form of the disease, with a case fatality rate of 20 to 40%. Early clinical manifestations are often difficult to distinguish from more common but less serious illness such as influenza. IMD outbreaks in the U.S. represent a small portion of the occurrence of IMD; 95 to 97% of IMD occurs in sporadic cases. (12) (13)

Humans are the only identified reservoir and vector of *N. meningitidis*. In most cases carriage is asymptomatic, but healthy carriers may spread the bacteria in respiratory droplets to others who are susceptible to invasive meningococcal disease. *N. meningitidis* is believed normally to be present in the nasopharynx of 10 to 25% of the population, though this carriage rate may be much higher in epidemics. (14)

There are 5 serogroups (A, B, C, Y and W-135) that are responsible for nearly all endemic and epidemic disease around the world. The global and Canadian epidemiology of IMD is dynamic with the dominant serogroups constantly changing. (15)

In the United States, the proportion of cases caused by serogroup Y increased significantly from 2% in 1989-1991 to approximately one third of cases affecting all age groups. Serogroup Y has been reported to cause outbreaks in military personnel and in nursing homes. (12)

Meningitis caused by serogroup W-135 is regarded as an emerging disease. In 2000 and 2001, global outbreaks of W-135 were associated with a hyper-virulent clone. The attack rate in close contacts of carriers was estimated to be 18 to 28 per 100,000. Eight percent of close contacts became carriers of the W-135 clone. In the same trial, 55% of carriers were still carriers of the W-135 strain six months later. The lengthy carriage, high transmissibility and virulence are risk factors which raise concern about the public health consequences and potential for future

epidemics. A massive outbreak of W-135 occurred in Africa in Burkina-Faso where it caused more than 10,000 cases in 2002. (16) (17)

The annual incidence of IMD in Canada has ranged between 0.5 and 2.1 per 100, 000 since the 1950s. Over the period 1995-2006, an average of 235 cases of IMD were reported annually. Using the 12-year average, the highest incidence is observed in infants less than 1 year of age (8.7 cases per 100 000), followed by children 1 through 4 years of age (2.3 per 100,000). The rates decrease in older children until adolescence and peak again in 15 through 19 year-olds (1.9 per 100,000) and 20 through 24 year-olds (1.0 per 100,000). Outbreaks of serogroup C were fairly common in the past. Between 1999 and 2001, 8 outbreaks of serogroup C meningococcal disease occurred in Canada. In more recent years, there has been a significant decline in incidence of serogroup C IMD. After serogroup C, serogroup B has caused the second highest burden of disease in Canada. Rates are particularly high in infants and children less than 4 years of age, but disease can occur at any age. Rates and numbers of serogroup Y IMD have remained stable over time. Although cases of serogroup Y IMD were reported in children and adolescents, most involved adults over the age of 25 years (median of 44 years of age during the period 1995 to 2006). IMD due to serogroups W-135 and A remains rare in Canada. (18) (19)

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Vaccine Information Service: 1-888-621-1146 or 416-667-2779. Business hours: 8 a.m. to 5 p.m. Eastern Time, Monday to Friday.

Full product monograph available on request or visit us at www.sanofipasteur.ca

Product information as of June 2012.

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Sanofi Pasteur Inc.
Swiftwater, PA, 18370 USA

Distributed by:
Sanofi Pasteur Limited
Toronto, Ontario, Canada

R5-0612 Canada

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

Menactra®

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

This leaflet is Part III of a three-part "Product Monograph" published when Menactra® was approved for sale in Canada. It gives you a summary of important information about Menactra®. It does not tell you everything about the vaccine. Contact your doctor, nurse or pharmacist if you have any questions**.**

ABOUT THIS VACCINE

What the vaccine is used for:

Menactra® is a vaccine that is used to prevent meningococcal diseases and/or septicemia (blood poisoning) caused by bacteria called *Neisseria meningitidis* (serogroups A, C, Y and W-135). This vaccine may be given to persons 9 months through 55 years of age.

Meningococcal diseases are very serious. Approximately 10% of people who get a meningococcal disease will die. Death may occur within 24-48 hours after symptoms appear. Of those who survive the disease, some (11 to 19%) will be permanently disabled. There are three kinds of meningococcal disease: meningococcemia, meningococcal meningitis and meningococcal pneumonia. Meningococcemia is the most serious form of the disease where up to 40% of those affected die.

What it does:

Menactra® causes your body to produce its own natural protection against meningococcal diseases. After you receive the vaccine, your body begins to make substances called antibodies. Antibodies help your body to fight disease. If a vaccinated person comes into contact with one of the germs that cause this disease, the body is usually ready to destroy it.

The amount of time it takes for your body to develop enough antibodies to protect you from meningococcal diseases can vary. It can take several days to a few weeks after your vaccination.

The great majority of people who get vaccinated with Menactra® will produce enough antibodies to protect them against meningococcal diseases (groups A, C, Y and W-135). However, as with all vaccines, 100% protection cannot be guaranteed.

When it should not be used:

Do not give Menactra® to:

- persons who are known to have a severe allergy to any ingredient in the vaccine or its container, or who have had a severe allergic reaction after receiving a vaccine that contained similar ingredients.

What the medicinal ingredient is:

Each 0.5 mL dose of Menactra® contains: meningococcal A, C, Y and W-135 polysaccharides conjugated to diphtheria toxoid protein carrier.

What the important non-medicinal ingredients are:

The stopper for the single dose vial does not contain dry natural rubber latex.

What dosage forms it comes in:

Menactra® is a liquid vaccine that is injected into a muscle. A single dose is 0.5 mL.

WARNINGS AND PRECAUTIONS

If you or your child has any of the following conditions, talk to your doctor or nurse BEFORE you or your child receives Menactra®:

- **A high fever or serious illness.** Delay the vaccination until the person is better.
- **An allergy to any component of the vaccine or the container.**

- **Pregnant or nursing women.** It is important that you understand the risks and benefits of vaccination. Menactra® should be given to a pregnant woman only if it is clearly needed. Tell the person giving you the injection if you are pregnant or breast-feeding.

- **A weakened immune system.** The vaccine may provide you with a lower level of protection than it does for people with healthy immune systems. If possible, try to postpone the vaccination until after you have completed the treatment that affects your immune system.

- **A bleeding disorder or taking blood-thinning medications.** Tell the person giving you the injection about your condition. The injection must be done carefully to prevent excessive bleeding.

- **A previous history of a serious nervous system disorder called Guillain-Barré syndrome (GBS).** These persons may be at increased risk of GBS after receiving Menactra®.

If removal of the spleen (splenectomy) is planned, Menactra® should be given, if possible, 10 to 14 days before surgery.

INTERACTIONS WITH THIS VACCINE

DO NOT mix Menactra® with other vaccines or medicinal products in the same syringe.

Menactra® may be given at the same time but at separate sites with:

- tetanus and reduced-dose diphtheria vaccine
- *Salmonella typhi* Vi Capsular Polysaccharide Vaccine
- Measles, Mumps, Rubella, Varicella vaccines
- Pneumococcal conjugate vaccine
- Hepatitis A vaccine
- *Haemophilus influenzae* type b vaccine

PROPER USE OF THIS VACCINE

For infants and toddlers 9 months of age through 23 months of age, 2 single doses (0.5 mL) given at least 3 months apart are recommended. For persons 2 years of age and over, a single dose (0.5 mL) is recommended.

The vaccination should be given in the muscle, preferably in the deltoid (shoulder) region.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Not applicable to this vaccine.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

A vaccine, like any medicine, may cause serious problems, such as severe allergic reactions. The risk of Menactra® causing serious harm is extremely small. The small risks associated with Menactra® are much less than the risks associated with getting the disease.

Tell your doctor, nurse or pharmacist as soon as possible if you do not feel well after having Menactra®.

Serious side effects are extremely rare.

Some people who receive Menactra® may have mild side effects such as redness or pain at the site of injection, headache or fever. Common side effects in infants include fever, increased crying, fussiness, vomiting, drowsiness and loss of appetite. These side effects usually go away within a few days.

This is not a complete list of side effects. For any unexpected effects while taking Menactra®, contact your doctor or pharmacist.

HOW TO STORE IT

Store the vaccine in a refrigerator at 2° to 8°C (35° to 46°F). **Do not freeze.** Throw away the product if it has been exposed to freezing.

Do not use after the expiration date.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects information on serious and unexpected adverse events following vaccination. If you suspect you have had a serious or unexpected event following receipt of a vaccine you may notify the Public Health Agency of Canada:

By toll-free telephone: 613-954-5590
(1-866-844-0018)
By toll-free fax: 613-954-9874
(1-866-844-5931)
By email: caefi@phac-aspc.gc.ca

By regular mail:
The Vaccine Safety Section
Centre for Immunization & Respiratory Infectious Diseases
Public Health Agency of Canada
130 Colonnade Road
A/L 6502A,
Ottawa, Ontario
K1A 0K9

Note: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.sanofipasteur.ca

You may also contact the vaccine producer, Sanofi Pasteur Limited, for more information.

Telephone: 1-888-621-1146 (no charge) or 416-667-2779 (Toronto area).
Business hours: 8 a.m. to 5 p.m. Eastern Time, Monday to Friday.

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