PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

MenQuadfi™

Meningococcal (Groups A, C, Y, W) Polysaccharide Tetanus Toxoid Conjugate Vaccine

Solution for injection, 0.5mL single dose vial for intramuscular injection

Active Immunizing Agent for the Prevention of Invasive Meningococcal Disease

ATC code: J07AH08

Sanofi Pasteur Limited

Toronto, Ontario, Canada

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RECENT MAJOR LABEL CHANGES

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

MenQuadfi™ is indicated for active immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W and Y in individuals 12 months of age and older.

MenQuadfi does not prevent *N. meningitidis* serogroup B disease.

1.1 Pediatrics

Pediatrics (≥12 months of age): Based on the data submitted and reviewed by Health Canada, the safety and immunogenicity of MenQuadfi in pediatrics has been established; therefore, Health Canada has authorized an indication for pediatric use. (see WARNINGS and PRECAUTIONS, Pediatrics).

1.2 Geriatrics

Geriatrics (≥65 years of age): Based on the data submitted and reviewed by Health Canada, the safety and immunogenicity of MenQuadfi in geriatrics has been established; therefore, Health Canada has authorized an indication for geriatric use.

2 CONTRAINDICATIONS

MenQuadfi is contraindicated in anyone with a known systemic hypersensitivity reaction to any component of MenQuadfi, including tetanus toxoid, or after a previous administration of the vaccine. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING and WARNINGS AND PRECAUTIONS.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Primary Vaccination:
Individuals 12 months of age and older receive a single dose (see Clinical Trials).

Booster Vaccination:

- A single dose of MenQuadfi may be administered to adolescents and adults who are at continued risk for meningococcal disease if at least 4 years have elapsed since a prior dose of meningococcal (Groups A, C, W, Y) conjugate vaccine (see CLINICAL TRIALS, Booster).
- There are no data available yet to indicate the need for or timing of a booster dose of MenQuadfi for individuals who have been primed with MenQuadfi.

4.4 Administration

MenQuadfi is a ready to use clear, colourless solution. The vaccine should be inspected visually for any particulate matter and/or variation of physical aspect prior to administration. Do not use if the content appears otherwise. Discard any unused portion.

MenQuadfi should be administered as a single 0.5 mL injection by intramuscular route into the deltoid region or anterolateral thigh, depending on the recipient's age and muscle mass. No data are available to establish safety and immunogenicity of the vaccine using intradermal or subcutaneous routes of administration.

Refer to DRUG INTERACTIONS section for concomitant administration with other vaccines.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form	Non-medicinal Ingredients
Intramuscular injection	Solution for injection (0.5 mL single dose vial)	Sodium Chloride, 50 mM Sodium Acetate, pH 6.0, Sterile Water for Injection

Description

MenQuadfi is a clear, colourless sterile liquid vaccine administered by intramuscular injection that contains *Neisseria meningitidis* serogroup A, C, W and Y capsular polysaccharide antigens individually conjugated to tetanus toxoid protein prepared from cultures of *Clostridium tetani*. *N. meningitidis* A, C, W and Y strains are cultured on Mueller Hinton agar medium and grown in Watson Scherp agar medium. The polysaccharides are extracted from the *N. meningitidis* cells and purified by centrifugation, detergent precipitation, alcohol precipitation, solvent extraction, and diafiltration. To prepare the polysaccharides for conjugation, Serogroup A is activated with carbonyldiimidazole (CDI), derivatized with adipic acid dihydrazide (ADH), and purified by diafiltration. Serogroups C, W, and Y are depolymerized, activated with periodate, and purified by diafiltration.

Clostridium tetani is fermented in media to generate tetanus toxin, which is purified by ammonium sulfate precipitation to yield purified tetanus toxin (PTT) and detoxified with formaldehyde to yield purified tetanus protein (PTP). The PTP is then concentrated and filtered to yield concentrated tetanus protein (CTP).

No preservative or adjuvant is added during manufacture.

Composition

The composition and function of each component contained within the 0.5 mL single dose are provided in Table 2

Table 2: Composition of the Drug Product

Component	Formulated Quantity (0.5 mL Dose)	Function
N. meningitidis Serogroup A Polysaccharide Concentrate (Conjugated to Tetanus Toxoid Protein)	10 mcg	*Active ingredient*
N. meningitidis Serogroup C Polysaccharide Concentrate (Conjugated to Tetanus Toxoid Protein)	10 mcg	*Active ingredient*
N. meningitidis Serogroup Y Polysaccharide Concentrate (Conjugated to Tetanus Toxoid Protein)	10 mcg	*Active ingredient*
N. meningitidis Serogroup W Polysaccharide Concentrate (Conjugated to Tetanus Toxoid Protein)	10 mcg	*Active ingredient*
Tetanus Toxoid Protein	55 mcg[1]	*Carrier Protein for all serogroup polysaccharide conjugates*
Sodium Chloride, USP	3.35 mg	*Excipient used to create an isotonic solution, (Inactive ingredient)*
50 mM Sodium Acetate, pH 6.0	0.3 mL	*Excipient used to maintain pH (Inactive ingredient)*
Sterile Water for Injection	QS to 0.5 mL	---

USP: United States Pharmacopoeia
QS: Quantity Sufficient

Packaging

The vaccine is manufactured as a 0.5 mL single dose unit. See Table 3.

Table 3: Final Product Container

Containers and Devices	Container Element	Nature
Single dose vial	Vial	USP Type I borosilicate glass Ammonium sulfate treated on inner surface
Vial Stopper	Chlorobutyl Stopper (not made with natural latex)	Chlorobutyl Synthetic Polyisoprene Blend
Seal	natural aluminum seal with white plastic flip cap	Aluminum and Homopolymer Polypropylene

7 WARNINGS AND PRECAUTIONS

Febrile illness

As with other vaccines, vaccination with MenQuadfi should be postponed in individuals suffering from an acute severe febrile illness. However, the presence of a minor infection, such as cold, is not a contraindication and should not result in the deferral of vaccination.

[1] Tetanus toxoid quantity is approximate and dependent on the polysaccharide to protein ratio for the conjugates used in each formulation

Guillain-Barré syndrome (GBS)

MenQuadfi should not be administered to subjects with a known history of Guillain-Barré syndrome, unless the potential benefits outweigh the risks of administration.

Hematologic

As with other vaccines administered intramuscularly, MenQuadfi should be given with caution to individuals with thrombocytopenia or any coagulation disorder or to individuals receiving anticoagulant therapy because of the risk of hematoma, and only if the potential benefit clearly outweighs the risk of administration.

Management of Acute Allergic Reactions

Appropriate observation and medical treatment should always be readily available in case of an anaphylactic event following the administration of the vaccine.

Protection

As with any vaccine, vaccination with MenQuadfi may not protect all vaccine recipients.

Syncope

Syncope can occur following or even before any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent falling and injury and to manage syncope.

Altered Immunocompetence

Reduced Immune Response: Some individuals with altered immunocompetence, including some individuals receiving immunosuppressant therapy, may have reduced immune responses to MenQuadfi.

Complement Deficiency: Persons with certain complement deficiencies and persons receiving treatment that inhibits terminal complement activation (for example, eculizumab) are at increased risk for invasive disease caused by *N. meningitidis*, including invasive disease caused by serogroups A, C, Y, and W, even if they develop antibodies following vaccination with MenQuadfi (See ACTION AND CLINICAL PHARMACOLOGY).

Tetanus Immunization

Immunization with MenQuadfi vaccine does not substitute for routine tetanus immunization.

Driving and Operating Machinery

MenQuadfi has no or negligible influence on the ability to drive and use machines. However, some of the effects may temporarily affect the ability to drive or use machines.

7.1 Special Populations

7.1.1 Pregnant Women

There are no clinical studies of MenQuadfi in pregnant women. Available human data cannot draw conclusions regarding whether or not MenQuadfi is safe for use during pregnancy.

A developmental and reproductive toxicity study in female rabbits showed no adverse effects on embryo-fetal development (including an evaluation of teratogenicity) or early post-natal development (Section NONCLINICAL TOXICOLOGY).

MenQuadfi should be used during pregnancy only if the potential benefits to the mother outweigh the potential risks, including those to the fetus.

7.1.2 Breast-feeding

There are no available data on the presence of MenQuadfi in human milk, milk production, or the effects on the breastfed infant. No conclusions can be drawn regarding whether or not MenQuadfi is safe for use during breastfeeding. MenQuadfi should be used during breastfeeding only if the potential benefits to the mother outweigh the potential risks, including those to the breastfed child.

7.1.3 Pediatrics

Pediatrics (< 12 months of age): Safety and immunogenicity of MenQuadfi has not been established in individuals less than 12 months of age.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following CIOMS frequency rating is used, when applicable:

Very common $\geq$ 10%;

Common $\geq$ 1 and $<$ 10%;

Uncommon $\geq$ 0.1 and $<$ 1%;

Rare $\geq$ 0.01 and $<$ 0.1%;

Very rare $<$ 0.01%;

Not known (cannot be estimated from available data).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse 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 reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of MenQuadfi in individuals 12 months of age and older is based on 7 pivotal clinical studies in which participants received either MenQuadfi alone (5,327 participants), MenQuadfi concomitantly with other vaccines (981 participants), the concomitant vaccines without MenQuadfi (590 participants), or a comparator meningococcal vaccine (2,898 participants).

In one of the concomitant trials, MenQuadfi was given with M-M-R®II (MMR) (Measles, Mumps, and Rubella Virus Vaccine Live, Merck & Co., Inc.); VARIVAX® (V) (Varicella Virus Vaccine Live,

Merck, Sharp & Dohme); Hexaxim® (DTaP-IPV-HB-Hib) (Diphtheria, tetanus, acellular pertussis components, hepatitis B, inactivated poliomyelitis, *Haemophilus influenzae* type b conjugate vaccine (adsorbed), Sanofi Pasteur SA); and Prevenar 13® (PCV) (Pneumococcal 13-valent Diphtheria CRM197 Protein Conjugate Vaccine, Pfizer Ireland Pharmaceuticals). In another trial, MenQuadfi was given concomitantly with Adacel® (Tdap) (tetanus toxoid, diphtheria toxoid, and pertussis, Sanofi Pasteur) and Gardasil® (quadrivalent human papillomavirus (HPV) vaccine, Merck). The comparator meningococcal vaccine was either Menactra® (MenACWY-DT) (Meningococcal Groups A, C, Y, and W-135 Polysaccharide Diphtheria Toxoid Conjugate Vaccine, Sanofi Pasteur) (1,042 participants), Menveo® (MenACWY-CRM) (Meningococcal Groups A, C, Y, and W-135 Oligosaccharide Diphtheria CRM197 Conjugate Vaccine, GSK Vaccines) (995 participants), Menomune® (MenACWY-PS) (Meningococcal Polysaccharide Vaccine, Groups A, C, Y, and W-135 Combined, Sanofi Pasteur) (453 participants) or with Nimenrix® (Polysaccharide Tetanus Toxoid Conjugate Vaccine Groups A, C, Y, and W-135, Pfizer) (408 participants).

Participants were enrolled at US, Puerto Rico, Mexico, Spain, Germany, Finland, Hungary, Russian Federation, Thailand and South Korea sites. Six of these studies evaluated the safety of a single dose of MenQuadfi (5,591 participants) in meningococcal vaccine-naïve participants. One of the six studies (MET51) additionally evaluated the safety of a single dose of MenQuadfi in a portion of participants (203) who had received a dose of meningococcal C conjugate vaccine in first year of life. The seventh study, (MET56), evaluated the safety of a single dose of MenQuadfi (402 participants) as a booster dose in a population that had received Menactra or Menveo 4 to 10 years earlier.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Safety in participants 12 through 23 months of age

The safety of MenQuadfi in participants 12 months through 23 months of age who were either meningococcal vaccine naïve or who had received monovalent meningococcal C conjugate (MenC) vaccination during infancy was evaluated in a randomized, active-controlled, modified double-blind trial (MET51). The safety analysis set included 303 meningococcal vaccine naïve participants who received MenQuadfi and 306 meningococcal vaccine naïve participants who received a comparator meningococcal vaccine (Nimenrix). The meningococcal vaccine naïve participants 12 months through 23 months of age who received MenQuadfi were a mean age of 16.0 months.

The rates and severity of the solicited adverse reactions that occurred within seven days following MenQuadfi compared with Nimenrix are presented in Table 4.

Unsolicited injection-site reactions at the site of MenQuadfi injection included bruising, haematoma, induration, pruritus, and rash (0.3% each). Unsolicited systemic adverse reactions assessed as vaccine-related by the investigator more than once among recipient of MenQuadfi and with a frequency of at least 1% (regardless of causal relationship) included diarrhea (MenQuadfi 7.6%, Nimenrix 5.2%).

SAEs occurred at a rate of 0.7% following MenQuadfi and at a rate of 0.3% following Nimenrix during the entire study period. No SAEs were determined to be vaccine-related.

Table 4: Percentages of Solicited Injection-Site Reactions and Systemic Reactions within 7 Days after Vaccination with MenQuadfi or Nimenrix, in Meningococcal Vaccine Naïve Participants 12 through 23 Months of Age (MET51)

	MenQuadfi (N†=303) Percentage		Nimenrix (N†=305) Percentage	
Adverse Reactions	**Any**	**Grade 3**	**Any**	**Grade 3**
Local Reactions				
Injection Site Pain‡	40.3	0.3	37.0	1.5
Injection Site Erythema§	40.3	4.3	37.7	2.3
Injection Site Swelling§	20.8	2.0	17.0	0.7
Systemic Reactions				
Fever¶	9.6	1.3	12.5	1.0
Vomiting†	6.9	0.0	4.3	0.0
Abnormal Crying*	35.0	2.0	36.1	2.3
Drowsiness#	21.1	0.3	18.0	0.0
Appetit lost±	29.7	0.7	30.5	0.7
Irritability!	47.5	1.0	41.6	1.6

† N is the number of vaccinated participants with available data for the events listed
‡ Grade 3: Cries when injected limb is moved, or the movement of the injected limb is reduced
§ Grade 3: > 50 mm
¶ Grade 3: ≥ 103.1°F (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 in participants 2 through 9 years of age

The safety of MenQuadfi in participants 2 years through 9 years of age was evaluated in a randomized, active controlled, modified double-blind study MET35. The safety analysis set included 498 participants who received MenQuadfi and 494 participants who received a comparator meningococcal vaccine (Menveo). The participants 2 years through 9 years of age who received MenQuadfi were a mean age of 6.0 years.

The rates and severity of the solicited adverse reactions that occurred within seven days following MenQuadfi compared with Menveo are presented in Table 5.

Unsolicited injection-site reactions at the site of MenQuadfi injection included bruising (0.4%), induration (0.2%), and warmth (0.2%). Unsolicited systemic adverse reactions assessed as vaccine-related by the investigator more than once among recipient of MenQuadfi and with a frequency of at least 1% (regardless of causal relationship) included vomiting (MenQuadfi 2.4%, Menveo 2.2%) and stomach pain (MenQuadfi 1.4%, Menveo 1.0%).

SAEs occurred at a rate of 1.4% following MenQuadfi and at a rate of 0.6% following Menveo during the entire study period. No SAEs were determined to be vaccine-related.

Table 5: Percentages of Solicited Injection-Site Reactions and Systemic Reactions within 7 Days after Vaccination with MenQuadfi or Menveo, in Participants 2 through 9 Years of Age (MET35)

	MenQuadfi (N†=484-487) %		Menveo (N†=479-486) %	
Adverse Reactions	**Any**	**Grade 3**	**Any**	**Grade 3**
Local Reactions				
Injection Site Pain‡	38.6	0.6	42.4	1.0
Injection Site Erythema§	22.6	3.1	31.5	9.9
Injection Site Swelling§	13.8	1.4	21.5	5.6
Systemic Reactions				
Myalgia¶	20.1	0.4	23.0	0.8
Malaise¶	21.1	1.8	20.4	1.0
Headache¶	12.5	0.0	11.5	0.4
Fever#	1.9	0.0	2.7	0.4

† N is the number of vaccinated participants with available data for the events listed
‡ Grade 3: Unable to perform usual activities
§ Any: > 0 mm; Grade 3: ≥ 50 mm
¶ Grade 3: Prevents daily activity
# Any: ≥ 100.4°F (38.0°C); Grade 3: ≥ 102.1°F (39.0°C)

Safety in participants 10 through 17 years of age

The safety of MenQuadfi in participants 10 years through 17 years of age was evaluated in two randomized, controlled clinical trials (MET43 and MET50). The safety analysis set in these two studies included 2,076 participants who received MenQuadfi alone (1,684 participants), MenQuadfi concomitant with other vaccines (392 participants), the concomitant vaccines without MenQuadfi (292 participants), or comparator meningococcal vaccine (824 participants). In the concomitant trial (MET50), MenQuadfi was given with vaccines containing tetanus toxoid, diphtheria toxoid, and pertussis (Tdap) and human papillomavirus (a quadrivalent HPV vaccine). The comparator meningococcal vaccine was either Menveo (501 participants) or Menactra (323 participants). The participants 10 years through 17 years of age who received MenQuadfi alone were a mean age of 11.9 years.

The rates and severity of the solicited adverse reactions that occurred within seven days following MenQuadfi alone compared with Menveo or Menactra are presented in Table 6.

Unsolicited injection-site reactions at the site of MenQuadfi injection with a frequency of at least 0.1% in either study MET50 when MenQuadfi was given alone or MET43 included pruritus (0.6% and 0.7%), rash (0.2% and 0.2%), warmth (0.8% and 0.5%), bruising (0.2% and <0.1%) and induration (0.0% and 0.2%). There were no unsolicited systemic adverse reactions assessed as vaccine-related by the investigator more than once among recipients of MenQuadfi and with a frequency of at least 1% (regardless of causal relationship).

SAEs occurred at a rate of 0.3%-0.8% following MenQuadfi alone and at a rate of 0.8% following Menveo in study (MET50) and 0.9% following Menactra in Study MET43 during the entire study period. No SAEs were determined to be vaccine-related. A few participants experienced dizziness

or syncope within 30 minutes following vaccination (MenQuadfi 0.2% [dizziness], Menveo 0.2% [syncope], Menactra 0.0%). These events were non-serious and spontaneously resolved on the same day.

Table 6: Percentages of Solicited Injection-Site Reactions and Systemic Reactions within 7 Days after Vaccination with MenQuadfi or Menveo (MET50) or to Menactra (MET43), in Participants 10 through 17 Years of Age

	MET50				MET43			
	MenQuadfi (N‡=494-496) %		Menveo (N‡=488-491) %		MenQuadfi (N‡=1129-1159) %		Menactra (N‡=310-314) %	
Adverse Reactions	**Any**	**Grade 3**	**Any**	**Grade 3**	**Any**	**Grade 3**	**Any**	**Grade 3**
Local Reactions								
Injection Site Pain§	45.2	1.4	42.5	1.0	34.8	1.8	41.4	2.2
Injection Site Erythema¶	5.0	0.4	7.5	1.2	4.5	0.3	4.5	0.3
Injection Site Swelling¶	5.4	0.2	6.5	0.4	4.1	<0.1	4.8	0.0
Systemic Reactions								
Myalgia§	35.3	1.6	35.2	1.8	27.4	1.9	31.2	1.9
Headache§	30.2	1.8	30.9	1.8	26.5	2.3	28.0	1.9
Malaise§	26.0	2.2	26.4	2.8	19.4	1.2	23.9	1.3
Fever#	1.4	0.4	1.2	0.6	0.7	0.2	0.6	0.0

‡ N is the number of vaccinated participants with available data for the events listed
§ Grade 3: Prevents daily activity
¶ Any: > 25 mm; Grade 3: > 100 mm
#Any: ≥ 100.4°F (38.0°C); Grade 3: ≥ 102.1°F (39.0°C)

Safety in participants 18 through 55 years of age

The safety of MenQuadfi in participants 18 years through 55 years of age was evaluated in a randomized, active-controlled, modified double-blind study MET43 conducted in the United States. The safety analysis set included 1,495 participants who received MenQuadfi and 312 participants who received a comparator vaccine (Menactra). The participants 18 years through 55 years of age who received MenQuadfi were a mean age of 39.4 years.

The rates and severity of the solicited adverse reactions that occurred within seven days following MenQuadfi compared with Menactra are presented in Table 7.

Unsolicited injection-site reactions at the site of MenQuadfi injection with a frequency of at least 0.1% included pruritus (0.8%), warmth (0.3%), and mass (0.1%). There were no unsolicited systemic adverse reactions assessed as vaccine-related by the investigator more than once among recipient of MenQuadfi and with a frequency of at least 1% (regardless of causal relationship).

A few participants experienced dizziness within 30 minutes following vaccination (MenQuadfi 0.3%, Menactra 0.3%). These events were non-serious and spontaneously resolved on the same day.

SAEs occurred at a rate of 1.6% following MenQuadfi and at a rate of 0.6% following Menactra during the entire study period. No SAEs were determined to be vaccine-related.

Table 7: Percentages of Solicited Injection-Site Reactions and Systemic Reactions within 7 Days after Vaccination with MenQuadfi or Menactra, in Participants 18 through 55 Years of Age (MET43)

	MenQuadfi (N†=1,441-1,460) %		Menactra (N†=297-301) %	
Adverse Reactions	**Any**	**Grade 3**	**Any**	**Grade 3**
Local Reactions				
Injection Site Pain‡	41.9	1.9	35.0	1.3
Injection Site Erythema§	5.1	0.3	3.7	0.3
Injection Site Swelling§	4.3	0.2	3.4	0.3
Systemic Reactions				
Myalgia‡	35.6	3.6	31.2	2.3
Headache‡	29.0	2.9	27.6	2.7
Malaise‡	22.9	2.9	18.9	3.3
Fever¶	1.4	0.1	1.7	0.7

† N is the number of vaccinated participants with available data for the events listed
‡ Grade 3: Prevents daily activity
§ Any: > 25 mm; Grade 3: > 100 mm
¶ Any: ≥ 100.4°F (38.0°C); Grade 3: ≥ 102.1°F (39.0°C)

Safety in participants 56 years of age and older

The safety of MenQuadfi in participants 56 years of age and older was evaluated in clinical trial (MET49) conducted in the United States. The safety analysis set included 448 participants who received MenQuadfi and 453 participants who received a quadrivalent polysaccharide meningococcal vaccine (Menomune) as comparator. As the route of administration differed for the two vaccines (MenQuadfi given intramuscularly, Menomune given subcutaneously), study personnel collecting the safety data differed from personnel administering the vaccine. The participants 56 years of age and older who received MenQuadfi were a mean age of 66.7 years. 46.1% of MenQuadfi recipients were 56 through 64 years of age; 53.9% were 65 years of age and older.

The rates and severity of the solicited adverse reactions that occurred within seven days following MenQuadfi compared with Menomune in study MET49 are presented in Table 8.

Unsolicited injection-site reactions at the site of MenQuadfi injection included pruritus (1.8%), warmth (0.2%) and ecchymosis (0.2%). There were no unsolicited systemic adverse reactions assessed as vaccine-related by the investigator more than once among recipient of MenQuadfi and with a frequency of at least 1% (regardless of causal relationship).

SAEs occurred at a rate of 3.3% following MenQuadfi and at a rate of 3.3% following Menomune during the entire study period. No SAEs were determined to be vaccine-related.

Table 8: Percentages of Solicited Injection-Site Reactions and Systemic Reactions within 7 Days after Vaccination with MenQuadfi or Menomune, in Participants 56 Years of Age and Older (MET49)

	MenQuadfi (N†=436-443) %		Menomune‡ (N†=449-451) %	
Adverse Reactions	**Any**	**Grade 3**	**Any**	**Grade 3**
Local Reactions				
Injection Site Pain§	25.5	0.7	9.6	0.7
Injection Site Erythema¶	5.2	0.2	0.0	0.0
Injection Site Swelling¶	4.5	0.0	0.0	0.0
Systemic Reactions				
Myalgia§	21.9	1.6	15.3	1.3
Headache§	19.0	0.7	14.6	0.7
Malaise§	14.5	1.4	11.3	1.8
Fever#	2.1	0.2	0.4	0.0

† N is the number of vaccinated participants with available data for the events listed
‡ Menomune was given subcutaneously
§ Grade 3: Prevents daily activity
¶ Any: > 25 mm; Grade 3: > 100 mm
# Any: ≥ 100.4°F (38.0°C); Grade 3: ≥ 102.1°F (39.0°C)

Studies in meningococcal vaccine-primed population

MenC primed individuals 12 through 23 months of age

The safety of MenQuadfi in participants 12 months through 23 months of age who were either meningococcal vaccine naïve or who had received monovalent MenC vaccination during infancy was evaluated in a randomized, active-controlled, modified double-blind trial MET51. The MenC-primed participants 12 months through 23 months of age who received MenQuadfi were a mean age of 14.0 months.

The rates and severity of the solicited adverse reactions that occurred within seven days following MenQuadfi compared with Nimenrix are presented in Table 9.

SAEs occurred at a rate of 1.0% following MenQuadfi and at a rate of 2.0% following Nimenrix during the entire study period. No SAEs were determined to be vaccine-related.

Table 9: Percentages of Solicited Injection-Site Reactions and Systemic Reactions within 7 Days after Vaccination with MenQuadfi or Nimenrix, in Monovalent MenC-Primed Participants 12 through 23 Months of Age (MET51)

	MenQuadfi (N†=203) Percentage		Nimenrix (N†=101-102) Percentage	
Adverse Reactions	**Any**	**Grade 3**	**Any**	**Grade 3**
Local Reactions				
Injection Site Pain‡	27.1	0.5	19.6	1.0
Injection Site Erythema§	25.6	2.0	20.6	0.0
Injection Site Swelling§	17.2	1.5	8.8	0.0
Systemic Reactions				
Fever¶	11.3	0.5	10.9	0.0
Vomiting†	9.4	0.5	6.9	0.0
Abnormal Crying*	23.6	0.5	22.5	0.0
Drowsiness#	25.1	1.5	18.6	0.0
Appetit lost±	27.6	2.0	27.5	0.0
Irritability!	37.4	1.5	35.3	1.0

† N is the number of vaccinated participants with available data for the events listed
‡ Grade 3: Cries when injected limb is moved, or the movement of the injected limb is reduced
§ Grade 3: > 50 mm
¶ Grade 3: ≥ 103.1°F (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

Individuals 15 years of age and older who have been previously vaccinated with either Menactra or Menveo

The safety of MenQuadfi in previously vaccinated participants 15 years of age and older was evaluated in a randomized, active controlled, modified double-blind study MET56. Participants had received a quadrivalent meningococcal conjugate vaccine (Menveo or Menactra**)** 4 to 10 years previously. The safety analysis set included 402 participants who received MenQuadfi and 407 participants who received a comparator meningococcal vaccine (Menactra). The participants who received MenQuadfi were a mean age of 20.0 years at time of booster.

The rates and severity of the solicited adverse reactions that occurred within seven days following MenQuadfi compared with Menactra are presented in Table 10. The majority of solicited reactions are Grade 1 or 2 and resolved within 3 days.

SAEs occurred at a rate of 1.2% following MenQuadfi and at a rate of 1.0% following Menactra during the entire study period. No SAEs were determined to be vaccine-related.

Table 10: Percentages of Solicited Injection-Site Reactions and Systemic Reactions within 7 Days after Vaccination with MenQuadfi or Menactra, in Participants 15 Years of Age and Older (MET56)

	MenQuadfi (N†=390-398) %		Menactra (N†=395-402) %	
Adverse Reactions	**Any**	**Grade 3**	**Any**	**Grade 3**
Local Reactions				
Injection Site Pain‡	44.7	1.0	48.8	2.0
Injection Site Erythema§	5.0	0.0	1.5	0.0
Injection Site Swelling§	4.0	0.0	0.7	0.0
Systemic Reactions				
Myalgia‡	36.7	2.0	38.8	2.2
Headache‡	37.9	2.3	33.3	3.5
Malaise‡	27.6	2.8	26.9	3.5
Fever¶	0.0	0.0	0.5	0.3

† N is the number of vaccinated participants with available data for the events listed
‡ Grade 3: Prevents daily activity
§ Grade 3: > 100 mm
¶ Grade 3: ≥ 102.1°F (39.0°C)

Concomitant administration

MenQuadfi in concomitant use with other pediatric vaccines

The safety of MenQuadfi administered concomitantly with other pediatric vaccines was evaluated in a randomized controlled, open-label trial MET57. A single dose of MenQuadfi was administered alone or concomitantly with the pediatric vaccine(s) in healthy toddlers in South Korea and Thailand (measles-mumps-rubella [MMR] and varicella [V]), Mexico (diphtheria, tetanus, acellular pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type-b [DTaP-IPV-HB-Hib] conjugate vaccine), and Russia (pneumococcal conjugate vaccine [PCV13]). A total of 1183 healthy, meningococcal-vaccine naïve toddlers aged 12 to 23 months were enrolled and randomized into 12 groups. This study also enrolled participants who received MMR+V, DTaP-IPV-HB-Hib, or PCV13 without MenQuadfi.

The rates of solicited local reactions at any vaccine injection site were comparable when MMR+V were given concomitantly with (52.9%) or without MenQuadfi (46.3%), and when DTaP-IPV-HB-Hib was given with (58.1%) or without MenQuadfi (65.3%). The rates of solicited local reactions at any vaccine injection site was higher in participants who received PCV13 given concomitantly with MenQuadfi (31.5%) than in participants who received PCV13 alone (13.1%).

The rates of solicited systemic reactions were comparable when MMR+V were given concomitantly with (46.6%) or without MenQuadfi (43.2%), and when DTaP-IPV-HB-Hib was given with (51.3%) or without MenQuadfi (50.5%). The rates of solicited systemic reactions was higher in participants who received PCV13 given concomitantly with MenQuadfi (20.0%) than in participants who received PCV13 alone (10.1%).

MenQuadfi in concomitant use with Tdap and HPV

The safety of MenQuadfi administered concomitantly with Adacel (Tdap) and Gardasil (a quadrivalent HPV) was evaluated in a randomized, controlled, open-label trial MET50. The safety analysis set included 895 participants who received MenQuadfi alone (503 participants), MenQuadfi concomitantly with Tdap and a quadrivalent HPV (392 participants), Tdap and a quadrivalent HPV without MenQuadfi (296 participants), or a comparator meningococcal vaccine (501 participants, Menveo). The participants 10 years through 17 years of age who received MenQuadfi concomitant with Tdap and a quadrivalent HPV were a mean age of 11.3 years.

The rates of solicited local reactions at any vaccine injection site and the rates of solicited systemic reactions were comparable when Tdap and quadrivalent HPV were given concomitantly with (84.5% and 70.6%, respectively) or without MenQuadfi (82.3% and 65.9%, respectively).

Solicited injection site reactions and systemic reactions when MenQuadfi was given alone occurred at a rate of 46.6% and 52.0%, respectively.

8.5 Post-Market Adverse Reactions

In addition to the adverse events observed during the clinical trials, the following events have been reported during the postmarketing use of MenQuadfi. The frequency is qualified as "not known" (cannot be estimated from available data).

- *Immune system disorders*: Hypersensitivity including anaphylaxis
- *Nervous system disorders*: Convulsions with or without fever

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Vaccine-Drug Interactions:

Immunosuppressive therapies (See 7 WARNINGS AND PRECAUTIONS).

Concomitant Administration with other Vaccines:

MenQuadfi should not be mixed with any other vaccine in the same vial.

If MenQuadfi needs to be given at the same time as another injectable vaccine(s), immunization should be carried out on separate limbs.

Lower geometric mean antibody concentrations (GMCs) for antibodies to the pertussis antigens filamentous hemagglutinin (FHA), pertactin (PRN) and fimbriae (FIM) were observed following Tdap vaccine administered concomitantly with MenQuadfi and a quadrivalent HPV versus Tdap vaccine administered concomitantly with a quadrivalent HPV vaccine. Because there are no established serological correlates of protection for pertussis, the clinical implications of the observed pertussis antigen responses are unknown.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Invasive meningococcal disease (IMD) is caused by the bacterium *N. meningitidis*, a gram-negative diplococcus found exclusively in humans. The presence of bactericidal anti-capsular meningococcal antibodies has been associated with protection from IMD. MenQuadfi induces the production of bactericidal antibodies specific to the capsular polysaccharides of *N. meningitidis* serogroups A, C, W and Y.

10.2 Pharmacodynamics

Refer to CLINICAL TRIALS section for immunogenicity.

10.3 Pharmacokinetics

No pharmacokinetic studies have been performed.

11 STORAGE, STABILITY AND DISPOSAL

Store at 2°C to 8°C. Do not freeze.

Do not use after expiration date shown on the label.

Any unused product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Meningococcal (Groups A, C, Y, W) Polysaccharide Tetanus Toxoid Conjugate Vaccine

Product Characteristics

MenQuadfi is a sterile solution of *Neisseria meningitidis* purified capsular polysaccharides of groups A, C, W and Y individually conjugated to tetanus toxoid protein prepared from cultures of *Clostridium tetani*.

MenQuadfi is a sterile liquid vaccine administered by intramuscular injection that contains *Neisseria meningitidis* serogroup A, C, W and Y capsular polysaccharide antigens individually conjugated to tetanus toxoid protein. *N. meningitidis* A, C, W and Y strains are cultured on Mueller Hinton agar medium and grown in Watson Scherp agar medium. The polysaccharides are extracted from the *N. meningitidis* cells and purified by centrifugation, detergent precipitation, alcohol precipitation, solvent extraction, and diafiltration. To prepare the polysaccharides for conjugation, Serogroup A is activated with carbonyldiimidazole (CDI), derivatized with adipic acid dihydrazide (ADH), and purified by diafiltration. Serogroups C, W, and Y are depolymerized, activated with periodate, and purified by diafiltration.

Clostridium tetani is fermented in media to generate tetanus toxin, which is purified by ammonium sulfate precipitation to yield purified tetanus toxin (PTT) and detoxified with formaldehyde to yield purified tetanus protein (PTP). The PTP is then concentrated and filtered to yield concentrated tetanus protein (CTP).

No preservative or adjuvant is added during manufacture.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The safety and immunogenicity of MenQuadfi in individuals 12 months of age and older is based on 7 pivotal clinical studies in which participants received either MenQuadfi alone (5,327 participants), MenQuadfi concomitantly with other vaccines (981 participants), the concomitant vaccines without MenQuadfi (590 participants), or a comparator meningococcal vaccine (2,898 participants).

Table 11: Clinical Studies with MenQuadfi

Trial Code	Trial Objectives	Age Group (mean age)	Trial Phase and Location	MenQuadfi	Comparator
				(Number of participants in the safety analysis set)	
MET51	Immunogenicity and safety	12-23 months of age (15 months of age)	Phase III in the European Union (EU)	MenQuadfi (506)	Nimenrix (408)
MET57	Immunogenicity and safety when given alone or concomitantly with MMR + Varicella, DTaP-IPV-HB-Hib, or PCV	12-23 months of age (15 months of age)	Phase III in South Korea, Thailand, Russian Federation, and Mexico	MenQuadfi alone (294)	N/A
				MenQuadfi + MMR + Varicella (189)	MMR + Varicella (95)
				MenQuadfi + DTaP-IPV-HB-Hib (200)	DTaP-IPV-HB-Hib (100)
				MenQuadfi + PCV (200)	PCV (99)
MET35	Immunogenicity and safety	2-9 years of age with subgroups 2-5 & 6-9 (6 years of age)	Phase III in US and Puerto Rico	MenQuadfi (498)	Menveo (494)
MET50	Immunogenicity and safety when given alone or concomitantly with Tdap and HPV	10-17 years of age (12 years of age - received MenQuadfi alone)	Phase II in US	MenQuadfi alone (503)	Menveo alone (501)
				MenQuadfi +Tdap +HPV (392)	Tdap +HPV (296)
MET43	Safety and immunogenicity	10-55 with subgroups 10-17 & 18-55 (40 years of age)	Phase III in US	MenQuadfi (2,676)	Menactra (635)
MET56	Immunogenicity and safety booster dose	>15 years of age (20 years of age)	Phase III in US and Puerto Rico	MenQuadfi (402)	Menactra (407)
MET49	Immunogenicity and safety	≥56 years with subgroups 56-64, 65-74 & ≥75 (67 years of age)	Phase III in US and Puerto Rico	MenQuadfi (448)	MenACWY polysaccharide (453)

14.2 Study Results

The immunogenicity of a single dose of MenQuadfi was assessed in 7 pivotal studies in participants from 12 months of age and older (see Table 11). Serum was collected at baseline and 30 days post vaccination to measure antibodies with a serum bactericidal assay using human complement (hSBA). The vaccine seroresponse rate, seroprotection rate and hSBA geometric mean titers (GMTs) were assessed as defined below unless specified otherwise.

- Seroprotection − proportions of participants with post-vaccination hSBA ≥ 1:8
- Geometric mean titers (GMTs)
- Vaccine seroresponse − was defined as: for a participant with a pre-vaccination titer < 1:8, the post-vaccination titer must be ≥ 1:16; for a participant with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.

Non-inferiority of MenQuadfi versus comparators was demonstrated in all studies for all 4 serogroups. Non-inferiority as assessed by vaccine seroresponse rates was demonstrated if the lower limit of the 2-sided 95% CI of the difference was > -10% for all 4 serogroups.

Overall, immunogenicity results using rabbit complement (rSBA) to measure SBA activity were consistent with what was observed with hSBA.

14.4 Immunogenicity

Immunogenicity in Individuals 12 to 23 months of age

Immunogenicity in participants 12 through 23 months of age was evaluated in MET51. This study was conducted in participants who were either meningococcal vaccine naive or had been primed with monovalent MenC vaccines (MenC-TT or MenC-CRM) in the first year of life. The participants were randomized to receive either a single dose of MenQuadfi or the licensed Nimenrix vaccine.

Non-inferiority of immune response based on percentage of subjects achieving a post-vaccination hSBA titer ≥ 1:8 at Day 30 was demonstrated for MenQuadfi versus Nimenrix vaccine for all serogroups. See Table 12.

Non-inferiority of immune response, based on percentage of subjects achieving a post-vaccination hSBA titer ≥ 1:8 at Day 30 in meningococcal vaccine naive participants, was also demonstrated for MenQuadfi versus Nimenrix vaccine for all serogroups. See Table 12.

The majority of meningococcal C vaccine primed participants (12-23 months of age) for study MET51, in the MenQuadfi group (N=198) (≥86.7%) and in Nimenrix group (N=99) (≥85.7%) had hSBA titers ≥1:8. These participants had received during their infancy either MenC-TT or MenC-CRM vaccines. In the subset of MenC-CRM primed participants, and for serogroup A only, the GMTs were lower in the MenQuadfi group (n=49) than in the Nimenrix group (n=25). The clinical significance of this observation is not known.

Table 12: Summary of hSBA vaccine seroprotection rate (≥1:8) (%) and GMTs to MenQuadfi and Nimenrix 30 Days after Vaccination of Participants 12 through 23 Months of Age - PPAS (MET51)

Endpoint†	Background	MenQuadfi (95% CI)	Nimenrix (95% CI)	Percent difference MenQuadfi minus Nimenrix‡ (95% CI)
A				
% Participants achieving hSBA ≥1:8	Naïve	90.8 (86.9; 93.8) N=293	89.5 (85.4; 92.7) N=295	-2.03 (-5.84; 1.78)
	MenC-Primed	89.8 (84.8; 93.7) N=197	98.0 (92.9; 99.8) N=99	
GMT	All	29.9 (26.9; 33.2) N = 490	34.5 (30.5; 39.0) N = 394	
C				
% Participants achieving hSBA ≥1:8	Naïve	99.3 (97.6; 99.9) N=293	81.4 (76.4; 85.6) N=295	12.1 (8.16; 16.1)
	MenC-Primed	99.0 (96.4; 99.9) N=196	98.0 (92.9; 99.8) N=99	
GMT	All	880 (748; 1035) N = 489	77.1 (60.7; 98.0) N = 394	
Y				
% Participants achieving hSBA ≥1:8	Naïve	93.2 (89.7; 95.8) N=293	91.6 (87.8; 94.5) N=296	2.42 (-1.34; 6.19)
	MenC-Primed	95.9 (92.2; 98.2) N=197	91.9 (84.7; 96.4) N=99	
GMT	All	41.7 (37.5; 46.5) N = 490	31.9 (28.4; 36.0) N = 395	
W				
% Participants achieving hSBA ≥1:8	Naïve	83.6 (78.9; 87.7) N=293	83.4 (78.7; 87.5) N=296	0.458 (-4.37; 5.28)
	MenC-Primed	86.7 (81.2; 91.1) N=196	85.7 (77.2; 92.0) N=98	
GMT	All	24.4 (21.8; 27.5) N = 489	17.7 (15.8; 19.8) N = 394	

† Seroprotection rate (primary end point) for each serogroup: the proportion of participants with an hSBA postvaccination titer ≥ 1:8.
‡ Overall non-inferiority would be demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups.

Endpoint†	Background	MenQuadfi (95% CI)	Nimenrix (95% CI)	Percent difference MenQuadfi minus Nimenrix‡ (95% CI)

N: number of participants in per-protocol analysis set with valid serology results.
95% CI of the single proportion calculated from the exact binomial method.
95% CI of the difference calculated from the Wald method.

Immunogenicity in Individuals 2 through 9 years of age

Immunogenicity in participants aged 2 years through 9 years was evaluated in a randomized, multicenter, active-controlled, modified, double blind clinical study (MET35).

The hSBA seroresponse rate and GMTs observed between the two vaccines administered are summarized for the Per Protocol Analysis Set (PPAS) in Table 13. The non-inferiority of the vaccine seroresponse for all four serogroups was demonstrated following a single dose of MenQuadfi compared to that of MENVEO® in children aged 2 to 9 years.

Table 13: Summary of hSBA vaccine seroresponse rate (%), percentage of patients achieving seroprotection and GMTs for MenQuadfi and Menveo 30 days after vaccination of Participants 2 through 9 years of age - PPAS (MET35)

Endpoint†	MenQuadfi (95% CI)	Menveo (95% CI)	Percent difference MenQuadfi minus Menveo‡ (95% CI)
A	N=455-456	N=458	
% Participants achieving Seroresponse	55.4 (50.7; 60.0)	47.8 (43.2; 52.5)	7.6 (1.1, 14.0)
% Participants achieving hSBA ≥1:8 (Seroprotection)	84.6 (79.3; 89.1) N=228	76.5 (70.3; 81.9) N=221	
GMT	25 (22; 28)	23 (20; 26)	
C	N=458	N=458-459	
% Participants achieving Seroresponse	95.2 (92.8; 97.0)	47.8 (43.2; 52.5)	47.4 (42.2, 52.2)
% Participants achieving hSBA ≥1:8 (Seroprotection)	97.4 (94.4; 99.0) N=229	64.6 (57.9; 70.8) N=223	
GMT	238 (209; 270)	17.0 (14; 20)	
Y	N=458	N=459	
% Participants achieving Seroresponse	91.5 (88.5; 93.9)	79.3 (75.3; 82.9)	12.2 (7.7, 16.7)
% Participants achieving hSBA≥1:8 (Seroprotection)	97.8 (95.0; 99.3) N=229	86.9 (81.8; 91.1) N=222	
GMT	69 (61; 77)	44 (38; 50)	
W	N=458	N=459	
% Participants achieving Seroresponse	78.8 (74.8; 82.5)	64.1 (59.5; 68.4)	14.8 (8.9, 20.5)
% Participants achieving hSBA≥1:8 (Seroprotection)	90.8 (86.3; 94.2) N=229	80.6 (74.8; 85.6) N=222	
GMT	38 (34; 42)	26 (23; 30)	

† Seroresponse rate (primary end point) for each serogroup: the proportion of participants with an hSBA pre-vaccination titer < 1:8 who achieved a post-vaccination titer ≥ 1:16, or pre-vaccination titer ≥ 1:8 who achieved a post-vaccination titer at least 4-fold greater than the pre-vaccination titer.
‡ Overall non-inferiority would be demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups.
N: number of participants in per-protocol analysis set with valid serology results.

Endpoint†	MenQuadfi (95% CI)	Menveo (95% CI)	Percent difference MenQuadfi minus Menveo‡ (95% CI)

95% CI of the single proportion calculated from the exact binomial method.
95% CI of the difference calculated from the Wilson Score method without continuity correction

Immunogenicity in Individuals 10 through 17 years of age

Immunogenicity in participants aged 10 through 17 years was evaluated in two randomized, multicenter, active controlled studies comparing immune responses following administration of MenQuadfi with either Menveo (MET50) or Menactra (MET43).

The first study, MET50 was conducted in healthy meningococcal vaccine naive male and female participants following administration with either MenQuadfi alone; Menveo alone; MenQuadfi co-administered with Adacel (Tdap) and Gardasil (a quadrivalent HPV); or Adacel (Tdap) and Gardasil (a quadrivalent HPV) alone.

Immune non-inferiority, based on seroresponse, was demonstrated for MenQuadfi as compared to Menveo for all four serogroups. The hSBA seroresponse rate and GMTs for the two vaccines administered are summarized below in Table 14.

Table 14: Summary of hSBA vaccine seroresponse rate (%), percentage of patients achieving seroprotection and GMTs for MenQuadfi and Menveo 30 days after vaccination of Participants 10 through 17 years of age - PPAS (MET50)

Endpoint†	MenQuadfi (95% CI)	Menveo (95% CI)	Percent difference MenQuadfi minus Menveo‡ (95% CI)
A	N=463	N=464	
% Participants achieving Seroresponse	75.6 (71.4; 79.4)	66.4 (61.9;70.7)	9.2 (3.4; 15.0)
% Participants achieving hSBA≥1:8 (Seroprotection)	93.5 (90.9; 95.6) N=463	82.8 (79.0; 86.1) N=464	
GMT	44 (39; 50)	35 (30; 41)	
C	N=462	N=463	
% Participants achieving Seroresponse	97.2 (95.2; 98.5)	72.6 (68.3;76.6)	24.6 (20.3; 29.0)
% Participants achieving hSBA≥1:8 (Seroprotection)	98.5 (96.9; 99.4) N=462	76.0 (71.9; 79.8) N=463	
GMT	387 (329; 456)	51 (41; 64)	
W	N=463	N=464	
% Participants achieving Seroresponse	86.2 (82.7; 89.2)	66.6 (62.1; 70.9)	19.6 (14.2; 24.8)
% Participants achieving hSBA≥1:8 (Seroprotection)	99.1 (97.8; 99.8) N=463	90.7 (87.7; 93.2) N=464	
GMT	87 (78; 97)	36 (32; 41)	
Y	N=462-463	N=464	
% Participants achieving Seroresponse	97.0 (95.0; 98.3)	80.8 (76.9; 84.3)	16.2 (12.3; 20.2)
% Participants achieving hSBA≥1:8 (Seroprotection)	97.2 (95.2; 98.5) N=463	83.2 (79.5; 86.5) N=464	
GMT	76 (66; 87)	28 (24; 32)	

† Seroresponse rate (primary end point) for each serogroup: post-vaccination hSBA titers ≥1:8 for participants with pre-vaccination hSBA titers < 1:8 or at least a 4-fold increase in hSBA titers from pre to post-vaccination for participants with pre-vaccination hSBA titers ≥1:8

‡ Overall non-inferiority would be demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups

N: number of participants in per-protocol analysis set with valid serology results.

Endpoint†	MenQuadfi (95% CI)	Menveo (95% CI)	Percent difference MenQuadfi minus Menveo‡ (95% CI)

95% CI of the single proportion calculated from the exact binomial method.
95% CI of the difference calculated from the Wilson Score method without continuity correction.

The second study (MET43), was performed to evaluate the immunogenicity of MenQuadfi compared to Menactra in participants 10 through 55 years of age.

In this study, for participants aged 10 through 17 years of age (N=1097-1098 for MenQuadfi and N=300 for Menactra), seroresponse rates for MenQuadfi were non-inferior to those of Menactra for all serogroups.

Immunogenicity in Individuals 18 through 55 years of age

Immunogenicity in participants from 18 through 55 years of age was evaluated in a randomized, multicenter, active controlled, modified double blind study (MET43) comparing MenQuadfi to Menactra.

In this study, for participants 18 through 55 years of age, the hSBA seroresponse rate and GMTs are presented in Table 15. Non-inferiority, based on seroresponse rates, was demonstrated for MenQuadfi as compared to Menactra for all four serogroups.

Table 15: Summary of hSBA vaccine seroresponse rate (%), percentage of patients achieving seroprotection and GMTs for MenQuadfi and Menactra 30 days after vaccination of Participants 18 through 55 years of age - PPAS (MET43)

Endpoint†	MenQuadfi (95% CI)	Menactra (95% CI)	Percent difference MenQuadfi minus Menactra‡ (95% CI)
A	N=1,406-1,408	N=293	
% Participants achieving Seroresponse	73.5 (71.2; 75.8)	53.9 (48.0; 59.7)	19.6 (13.5; 25.8)
% Participants achieving hSBA ≥1:8 (Seroprotection)	93.5 (92.1; 94.8) N=1,408	88.1 (83.8; 91.5) N=293	
GMT	106 (97; 117)	52 (43; 64)	
C	N=1,406-1,408	N=293	
% Participants achieving Seroresponse	83.4 (81.4; 85.3)	42.3 (36.6; 48.2)	41.1 (35.0; 46.9)
% Participants achieving hSBA ≥1:8 (Seroprotection)	93.5 (92.0; 94.7) N=1,408	77.8 (72.6; 82.4) N=293	
GMT	234 (210; 261)	37 (29; 49)	
W	N=1,408-1,410	N=293	
% Participants achieving Seroresponse	77.0 (74.7; 79.2)	50.2 (44.3; 56.0)	26.8 (20.7; 32.9)
% Participants achieving hSBA ≥1:8 (Seroprotection)	94.5 (93.2; 95.7) N=1,410	80.2 (75.2; 84.6) N=293	
GMT	76 (69; 83)	33 (26; 42)	
Y	N=1,408-1,410	N=293	
% Participants achieving Seroresponse	88.1 (86.3; 89.8)	60.8 (54.9; 66.4)	27.4 (21.7; 33.3)
% Participants achieving hSBA ≥1:8 (Seroprotection)	98.6 (97.8; 99.1) N=1,410	81.2 (76.3; 85.5) N=293	
GMT	219 (200; 239)	55 (42; 70)	

† Seroresponse rate (primary end point) for each serogroup: the proportion of participants with an hSBA pre-vaccination titer < 1:8 who achieved a post-vaccination titer ≥ 1:16, or pre-vaccination titer ≥ 1:8 who achieved a post-vaccination titer at least 4-fold greater than the pre-vaccination titer.
‡ The overall non-inferiority would be demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups.
N: number of participants in per-protocol analysis set with valid serology results.

Endpoint†	MenQuadfi (95% CI)	Menactra (95% CI)	Percent difference MenQuadfi minus Menactra‡ (95% CI)

95% CI of the single proportion calculated from the exact binomial method.
95% CI of the difference calculated from the Wilson Score method without continuity correction.

Immunogenicity in Individuals 56 years of age and above

Immunogenicity in participants ≥ 56 years of age was assessed in a randomized, multicenter, active controlled, modified double blind trial (MET49) comparing MenQuadfi to Menomune.

Participants were stratified by age category: 56 through 64 years of age (44.3%), 65 through 74 years of age (39.7%), and 75 years and older (15.9%). The overall mean age of participants who received MenQuadfi was 66.9 years; range: 56 through 96 years of age. The mean age for participants in the 56 through 64 years age stratum who received MenQuadfi was 60.4 years, the mean age for participants ≥ 65 years age stratum who received MenQuadfi was 72.2 years.

The hSBA seroresponse rate and GMTs are presented in Table 16. Non-inferiority of seroresponse rates was demonstrated for MenQuadfi as compared to Menomune for all four serogroups.

Table 16: Summary of hSBA vaccine seroresponse rate (%), percentage of patients achieving seroprotection and GMTs for MenQuadfi and Menomune 30 days after vaccination of Participants 56 years of age and above - PPAS (MET49)

Endpoint†	MenQuadfi (95% CI)	Menomune (95% CI)	Percent difference MenQuadfi minus Menomune‡ (95% CI)
A	N=433	N=431	
% Participants achieving Seroresponse	58.2 (53.4; 62.9)	42.5 (37.7; 47.3)	15.7 (9.08; 22.2)
% Participants achieving hSBA ≥1:8 (Seroprotection)	89.4 (86.1; 92.1) N=433	84.2 (80.4; 87.5) N=431	
GMT	55 (47; 65)	31 (27; 37)	
C	N=433	N=431	
% Participants achieving Seroresponse	77.1 (72.9; 81.0)	49.7 (44.8; 54.5)	27.5 (21.2; 33.5)
% Participants achieving hSBA ≥1:8 (Seroprotection)	90.1 (86.9; 92.7) N=433	71.0 (66.5; 75.2) N=431	
GMT	101 (84; 123)	25 (21; 30)	
Y	N=433	N=431	
% Participants achieving Seroresponse	74.4 (70.0; 78.4)	43.4 (38.7; 48.2)	31.0 (24.6; 37.0)
% Participants achieving hSBA ≥1:8 (Seroprotection)	91.7 (88.7; 94.1) N=433	67.7 (63.1; 72.1) N=431	
GMT	69 (59; 81)	21 (17; 25)	
W	N=433	N=431	
% Participants achieving Seroresponse	62.6 (57.8; 67.2)	44.8 (40.0; 49.6)	17.8 (11.2; 24.2)
% Participants achieving hSBA ≥1:8 (Seroprotection)	77.4 (73.1; 81.2) N=433	63.1 (58.4; 67.7) N=431	
GMT	28 (24; 33)	15 (13; 18)	

† Seroresponse rate (primary end point) for each serogroup: the proportion of participants with an hSBA pre-vaccination titer < 1:8 who achieved a post-vaccination titer ≥ 1:16, or pre-vaccination titer ≥ 1:8 who achieved a post-vaccination titer at least 4-fold greater than the pre-vaccination titer.

‡ The overall non-inferiority would be demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups.

N: number of participants in per-protocol analysis set with valid serology results.

95% CI of the single proportion calculated from the exact binomial method.

95% CI of the difference calculated from the Wilson Score method without continuity correction.

Immunogenicity of a Booster Dose

A randomized, multicenter, active controlled, modified double blind trial (MET56) compared the immunogenicity of a booster dose of MenQuadfi to a booster dose of Menactra in MenACWY conjugate vaccine (Menveo or Menactra) primed 4 to 10 years earlier in participants at least 15 years of age.

The hSBA seroresponse rate and GMTs are presented in Table 17. Non-inferiority, based on seroresponse rates, was demonstrated for MenQuadfi as compared to Menactra for all four serogroups (see Table 17).

Table 17: Summary of hSBA vaccine seroresponse rate (%), percentage of patients achieving seroprotection and GMTs for MenQuadfi and Menactra 30 days after vaccination of primed Participants 10 through 55 years of age - PPAS (MET56)

Endpoint†	MenQuadfi (95% CI)	Menactra (95% CI)	Percent difference MenQuadfi minus Menactra‡ (95% CI)
A	N=384	N=389	
% Participants achieving Seroresponse	92.2 (89.0; 94.7)	87.1 (83.4; 90.3)	5.0 (0.735; 9.38)
% Participants achieving hSBA ≥1:8 (Seroprotection)	100.0 (99.0; 100.0) N=384	99.0 (97.4; 99.7) N=389	
GMT	497 (436; 568)	296 (256; 343)	
C	N=384	N=389	
% Participants achieving Seroresponse	97.1 (94.9; 98.6)	91.8 (88.6; 94.3)	5.4 (2.16; 8.76)
% Participants achieving hSBA ≥1:8 (Seroprotection)	99.5 (98.1; 99.9) N=384	99.0 (97.4; 99.7) N=389	
GMT	2618 (2227; 3078)	599 (504; 711)	
Y	N=384	N=389	
% Participants achieving Seroresponse	97.4 (95.3; 98.7)	95.6 (93.1; 97.4)	1.8 (-0.907; 4.55)
% Participants achieving hSBA ≥1:8 (Seroprotection)	99.7 (98.6; 100.0) N=384	99.5 (98.2; 99.9) N=389	
GMT	2070 (1807; 2371)	811 (699; 941)	
W	N=384	N=389	
% Participants achieving Seroresponse	98.2 (96.3; 99.3)	90.7 (87.4; 93.4)	7.4 (4.30; 10.9)
% Participants achieving hSBA ≥1:8 (Seroprotection)	100.0 (99.0; 100.0) N=384	99.7 (98.6; 100.0) N=389	
GMT	1747 (1508; 2025)	723 (614; 853)	

† Seroresponse rate (primary end point) for each serogroup: the proportion of participants with an hSBA pre-vaccination titer < 1:8 who achieved a post-vaccination titer ≥ 1:16, or pre-vaccination titer ≥ 1:8 who achieved a post-vaccination titer at least 4-fold greater than the pre-vaccination titer.

‡ The overall non-inferiority would be demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups.

N: number of participants in per-protocol analysis set with valid serology results.

95% CI of the single proportion calculated from the exact binomial method.

Endpoint†	MenQuadfi (95% CI)	Menactra (95% CI)	Percent difference MenQuadfi minus Menactra‡ (95% CI)

95% CI of the difference calculated from the Wilson Score method without continuity correction.

Immunogenicity of Concomitantly Administered Vaccines

Study MET57 was performed in meningococcal vaccine naïve participants aged 12 to 23 months to evaluate the immunogenicity of MenQuadfi concomitantly administered with MMR vaccine, varicella vaccine, PCV13 vaccine, and DTaP-IPV-HB-Hib vaccine (containing pertussis PT and FHA) and showed no clinically relevant interference on antibody responses to each of the antigens. Overall, the seroprotection rates for meningococcal serogroups A, C, W, and Y (hSBA titers ≥1:8) or the seroprotection rates/ GMCs of other antigens were comparable when MenQuadfi or licensed paediatric vaccines (MMR+V, DTaP-IPV-HB-Hib, or PCV13) were given alone or concomitantly.

A Phase II Study (MET50) was performed in meningococcal naive children and adolescents 10 through 17 years of age, to evaluate the immunogenicity of MenQuadfi administered concomitantly with Tdap and a quadrivalent HPV vaccines. The anti-pertussis responses of the Tdap vaccine administered concomitantly with MenQuadfi and HPV vaccine versus Tdap vaccine administered concomitantly with HPV vaccine only were non-inferior for the PT antigen and did not meet non-inferiority for the FHA, PRN, FIM antigens. Vaccine Response rates for serogroups A, C, W and Y were comparable across both groups. Because there are no established serological correlates of protection for pertussis, the clinical implications of the observed pertussis antigen responses are unknown.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Non-clinical safety data revealed no adverse effects observed for MenQuadfi in a repeat-dose toxicity and local tolerance study in rat and a developmental and reproductive toxicity study in rabbits.

MenQuadfi has not been evaluated for carcinogenic or mutagenic potential or for impairment of fertility in males.

Reproductive and Developmental Toxicity

A developmental and reproductive toxicity study was performed in female rabbits. The animals were administered a full human dose of MenQuadfi (0.5 mL) on five occasions: 30 days and 10 days before mating, and gestation days 6, 12 and 27. The study showed no adverse effects on embryo-fetal development (including an evaluation of teratogenicity) or early post-natal development up to post-natal day 35.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

MenQuadfi™

Meningococcal (Groups A, C, Y, W) Polysaccharide Tetanus Toxoid Conjugate Vaccine

Read this carefully before you or your child receive **MenQuadfi.** This leaflet is a summary and will not tell you everything about this product. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **MenQuadfi**.

What is MenQuadfi used for?

MenQuadfi is a vaccine. It is used to help protect you or your children against infections caused by bacteria (germs) called "*Neisseria meningitides"* types A, C, W and Y. *Neisseria meningitidis* can be passed from person to person and can cause meningitis, an inflammation of the tissues that surround the brain and spinal cord, or septicemia, an infection of the blood. Both can result in serious disease with lasting effects and possibly death. MenQuadfi will not protect against disease caused by any other infectious agents.

How does MenQuadfi work?

MenQuadfi causes your body to produce its own natural protection against bacteria that can cause meningococcal diseases ("*Neisseria meningitides"* types A, C, W and Y). 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 a few weeks after your vaccination.

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

What are the ingredients in MenQuadfi?

Medicinal ingredients: Meningococcal (groups A, C, W and Y) polysaccharides conjugated to tetanus toxoid protein carrier.

Non-medicinal ingredients: Sodium Chloride, 50 mM Sodium Acetate (pH 6.0), Sterile Water for Injection.

MenQuadfi comes in the following dosage forms:

MenQuadfi is a clear, colourless liquid vaccine that is injected into a muscle. A single dose is 0.5 mL.

Do not receive MenQuadfi if you or your child:

- are allergic to active substances or any of the other ingredients in MenQuadfi. Symptoms may include rash, itching, difficulty breathing, shortness of breath or swelling of the face,

lips, throat, or tongue. If you are not sure if you are allergic, talk to your doctor, pharmacist or nurse before you receive MenQuadfi.

- are a person with a known history of Guillain-Barré Syndrome unless the potential benefits outweigh the risks of administration.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you or your child receive MenQuadfi. Talk about any health conditions or problems you or your child may have, including if you or your child:

- ever fainted from an injection. Fainting, sometimes with falling, can occur (mostly in adolescents and young adults) following, or even before, any injection with a needle.
- a disease weakening your body's natural defenses (immune system). Your response to vaccines may not be optimal.
- thrombocytopenia or bleeding disorders or receiving anticoagulant therapy.
- illness with high fever (over 38°C). There is no need to delay vaccination for a minor infection such as a cold. However, talk to your doctor, pharmacist or nurse first.
- pregnancy and/or breast-feeding

Tell your healthcare professional about all the medicines you or your child take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

MenQuadfi may not have an optimal effect if used with medicines that weaken the immune system such as high-dose corticosteroids or chemotherapy.

How to take MenQuadfi:

MenQuadfi is given by a doctor, pharmacist, or nurse as a 0.5 ml injection in the muscle in the upper arm or in the thigh depending on your age and muscle mass.

Usual dose:

A single dose is 0.5 mL.

Overdose:

If you think you, or a person you are caring for, have received too much MenQuadfi, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Not applicable to this vaccine.

What are possible side effects from using MenQuadfi?

Like all medicines, this vaccine can cause side effects, although not everybody gets them. These are not all the possible side effects you or your child may feel when taking MenQuadfi. If you experience any side effects not listed here, contact your healthcare professional.

The following side effects can be seen after the use of MenQuadfi in children 12-23 months of age.

Very common (may affect more than 1 in 10 people)
- Tenderness, redness, or swelling where the injection was given
- Feeling irritable
- Crying
- Loss of appetite
- Feeling drowsy

Common (may affect up to 1 in 10 people)
- Fever
- Vomiting
- Diarrhea

The following side effects may happen in children (2years of age and older), adolescents, adults and the elderly.

Very common (may affect more than 1 in 10 people)
- Pain where the injection was given
- Muscle pain
- Headache
- Generally feeling unwell

Common (may affect up to 1 in 10 people)
- Redness or swelling where the injection was given
- Fever

Uncommon (may affect up to 1 in 100 people)
- Itching, warmth, bruising or rash where the injection was given
- Vomiting
- Feeling dizzy
- Nausea
- Fatigue

The following side-effects can happen in any age-group.

Not Known (cannot be estimated from available data)
- Hypersensitivity including anaphylaxis
- Fits (convulsions) with or without fever

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you or your child experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and Sanofi Pasteur cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit.

Storage:

Store in a refrigerator (+2°C to +8°C).

Do not freeze.

Keep out of reach and sight of children.

If you want more information about MenQuadfi:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.sanofi.com/en/canada, or by calling 1-888-621-1146 (no charge).

This leaflet was prepared by Sanofi Pasteur Limited.

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