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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MENQUADFI® safely and effectively. See full prescribing information for MENQUADFI.

MenQuadfi, Meningococcal (Groups A, C, Y, W) Conjugate Vaccine

Solution for Intramuscular Injection

Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------

MenQuadfi is a vaccine indicated for active immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y. MenQuadfi is approved for use in individuals 2 years of age and older. (1)

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

----------DOSAGE AND ADMINISTRATION----------

0.5 mL dose for intramuscular injection. (2)

Primary Vaccination

- Individuals 2 years of age and older: a single dose.

Booster Vaccination

- A single dose of MenQuadfi may be administered to individuals 15 years of age and older 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.

----------DOSAGE FORMS AND STRENGTHS----------

Solution for injection in 0.5 mL single-dose vial. (3)

----------CONTRAINDICATIONS----------

Severe allergic reaction to any component of the vaccine, or after a previous dose of MenQuadfi or any other tetanus toxoid-containing vaccine. (4)

----------ADVERSE REACTIONS----------

Most commonly reported adverse reactions (≥10%) following a primary dose were as follows:

- Children 2 through 9 years of age, pain (38.6%), erythema (22.6%), and swelling (13.8%) at the injection site; malaise (21.1%), myalgia (20.1%), and headache (12.5%). (6)
- Adolescents aged 10 through 17 years of age, injection site pain (34.8%–45.2%), myalgia (27.4%–35.3%), headache (26.5%–30.2%), and malaise (19.4%–26.0%). (6)
- Adults aged 18 through 55 years, injection site pain (41.9%), myalgia (35.6%), headache (29.0%), and malaise (22.9%). (6)
- Adults 56 years of age and older, pain at the injection site (25.5%), myalgia (21.9%), headache (19.0%), and malaise (14.5%). (6)

In adolescents and adults, rates of solicited adverse reactions following a booster dose were comparable to those observed following primary vaccination. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

MenQuadfi® is a vaccine indicated for active immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y. MenQuadfi is indicated for use in individuals 2 years of age and older.

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

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

MenQuadfi is a clear, colorless solution.

Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration, whenever solution and container permit. If any of these conditions exist, the vaccine should not be administered. Discard the vial with any unused portion.

2.2 Dose and Schedule

Administer MenQuadfi as a single 0.5 mL injection intramuscularly.

Primary Vaccination

- Individuals 2 years of age and older receive a single dose.

Booster Vaccination

- A single dose of MenQuadfi may be administered to individuals 15 years of age and older 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.

3 DOSAGE FORMS AND STRENGTHS

MenQuadfi is a sterile solution for intramuscular injection supplied in 0.5 mL single-dose vials.

4 CONTRAINDICATIONS

Severe allergic reaction to any component of the vaccine, or after a previous dose of MenQuadfi or any other tetanus toxoid-containing vaccine [*see Description (11)*].

5 WARNINGS AND PRECAUTIONS

5.1 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.

5.2 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, W, and Y, even if they develop antibodies following vaccination with MenQuadfi [*see Clinical Pharmacology (12.1)*].

5.3 Syncope

Syncope (fainting) can occur following, or even before, vaccination with MenQuadfi.

Procedures should be in place to prevent falling and injury and to manage syncope.

5.4 Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) has been reported in temporal relationship following administration of another U.S.-licensed meningococcal quadrivalent polysaccharide conjugate vaccine. The decision by the healthcare professional to administer MenQuadfi to persons with a history of GBS should take into account the expected benefits and potential risks.

5.5 Tetanus Immunization

Immunization with MenQuadfi does not substitute for routine tetanus immunization.

5.6 Limitations of Vaccine Effectiveness

Vaccination with MenQuadfi may not protect all vaccine recipients.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial(s) of a vaccine cannot be directly compared to rates in the clinical trial(s) of another vaccine and may not reflect the rates observed in practice.

The safety of a single dose of MenQuadfi in individuals 2 years of age and older was evaluated in five randomized, active-controlled, multi-center clinical studies conducted in the US and Puerto Rico. In these studies, a total of 4,919 participants received either a primary dose (N = 4517) or a booster dose (N = 402) of MenQuadfi and were included in the safety analyses.

Safety Monitoring

Participants were monitored for immediate reactions for 30 minutes following vaccination while at the study site. Solicited injection site and systemic reactions were recorded by participants or by parents/guardians in a diary card at home daily for 7 days following vaccination. All unsolicited adverse events that occurred within 30 days following vaccination were recorded by participants or by parents/guardians and collected by the study site at the next visit. Unsolicited adverse events that were medically attended (i.e., visits to an emergency room, or an unexpected visit to a health care provider), and all serious adverse events (SAEs) were collected for at least 6 months after vaccination.

Primary Vaccination Studies

Children 2 through 9 years of age

The safety of MenQuadfi in children 2 years through 9 years of age was evaluated in Study 1 (NCT03077438). The safety analysis set included 498 participants who received MenQuadfi and 494 participants who received Menveo [Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine]. Of the participants 2 through 9 years of age who received MenQuadfi (N = 498), 50.2% were 2 through 5 years of age, 49.8% were 6 through 9 years of age, 49.0% were female, 80.5% were White, 13.3% were Black or African American, 0.4% were Asian, 5.2% were of other racial groups, and 22.9% were of Hispanic or Latino ethnicity. There were no substantive differences in demographic characteristics between the vaccine groups.

The rates and severity of the solicited adverse reactions that occurred within 7 days following MenQuadfi compared with Menveo (Study 1) are presented in Table 1.

SAEs occurred at a rate of 1.4% following MenQuadfi and at a rate of 0.6% following Menveo during the entire study period. Most SAEs occurred more than 30 days following vaccination and were commonly occurring events in the general population in this age group. No SAEs were determined to be vaccine related.

Table 1: Percentages of Solicited Injection-Site Reactions and Systemic Adverse Reactions within 7 Days after Vaccination with MenQuadfi or Menveo in Children 2 through 9 Years of Age (Study 1)*

	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

* Clinical trial identifier NCT03077438
† 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)

Adolescents 10 through 17 years of age

The safety of MenQuadfi in adolescents 10 through 17 years of age was evaluated in two clinical trial studies Study 2 (NCT02199691) and Study 3 (NCT02842853). The safety analysis set in these two studies included 3,196 participants who received MenQuadfi alone (1,684 participants), MenQuadfi concomitantly with Adacel® [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed] (Tdap) and Gardasil® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] (HPV) (392 participants), the concomitant vaccines without MenQuadfi (296 participants), or a U.S.-licensed comparator meningococcal vaccine (824 participants). The comparator meningococcal vaccine was either Menveo (501 participants) or Menactra® [Meningococcal (Groups A, C, Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] (323 participants).

Of the participants 10 through 17 years of age who received MenQuadfi (N = 1,684), 49.6% were female. Among those with reported race and ethnicity, 79.3% were White, 14.2% were Black or African American, 1.1% were Asian, 5.4% were of other racial groups, and 21.5% were of Hispanic or Latino ethnicity. Mean age was 11.9 years at time of administration. There were no substantive differences in demographic characteristics between the vaccine groups.

The rates and severity of the solicited adverse reactions that occurred within 7 days following MenQuadfi compared with Menveo and Menactra are presented in Table 2. The most common injection site and systemic reactions occurring after MenQuadfi administration (in Study 2 and Study 3) were injection site pain (45.2% and 34.8%) and myalgia (35.3% and 27.4%), respectively.

In Study 2, SAEs occurred at a rate of 0.8% following MenQuadfi and 0.8% following Menveo. In Study 3, SAEs occurred at a rate of 0.3% following MenQuadfi and 0.9% following Menactra. No SAEs were determined to be vaccine related.

Table 2: Percentages of Solicited Injection-Site Reactions and Systemic Adverse Reactions within 7 Days after Vaccination with MenQuadfi or Menveo in Individuals 10 through 17 Years of Age Study 2* and MenQuadfi or Menactra in Individuals 10 through 17 Years of Age Study 3†

	Study 2				Study 3			
	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

* Clinical trial identifier NCT02199691
† Clinical trial identifier NCT02842853
‡ 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)

Among 296 participants who received Tdap and HPV concomitantly (without MenQuadfi) and 392 participants who received MenQuadfi concomitantly with Tdap and HPV, there were no notable differences in the rates of systemic solicited adverse reactions within 7 days following vaccination.

Dizziness within 30 minutes following vaccination was experienced by 1 (0.2%) participant who received MenQuadfi in Study 2 (NCT02199691) and 2 (0.2%) participants who received MenQuadfi in Study 3 (NCT02842853). Three participants in Study 2 experienced syncope

within 30 minutes following vaccination: 1 (0.2%) participant who received Menveo, 1 (0.3%) participant who received MenQuadfi concomitantly with Tdap and HPV, and 1 (0.3%) participant who received Tdap and HPV concomitantly (without MenQuadfi). These events were non-serious and spontaneously resolved on the same day.

Adults 18 through 55 years of age

The safety of MenQuadfi in adults 18 through 55 years of age was evaluated in Study 3 (NCT02842853). The safety analysis set included 1,495 participants who received MenQuadfi and 312 participants who received Menactra. Of the participants 18 years through 55 years of age who received MenQuadfi (N = 1,495), 65.2% were female. Among those with reported race and ethnicity, 73.3% were White, 21.0% were Black or African American, 2.2% were Asian, 3.5% were of other racial groups, and 20.0% were of Hispanic or Latino ethnicity. Mean age was 39.4 years at time of administration.

The rates and severity of the solicited adverse reactions that occurred within 7 days following MenQuadfi compared with Menactra are presented in Table 3.

Dizziness within 30 minutes following vaccination was experienced by 5 (0.3%) participants who received MenQuadfi and 1 (0.3%) participant who received Menactra. 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 3: Percentages of Solicited Injection-Site Reactions and Systemic Adverse Reactions within 7 Days after Vaccination with MenQuadfi or Menactra in Individuals 18 through 55 Years of Age (Study 3)*

	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

	MenQuadfi (N†=1,441-1,460) %		Menactra (N†=297-301) %	
Adverse Reactions	Any	Grade 3	Any	Grade 3
Malaise‡	22.9	2.9	18.9	3.3
Fever¶	1.4	0.1	1.7	0.7

* Clinical trial identifier NCT02842853
† 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)

Adults 56 years of age and older

The safety of MenQuadfi in adults 56 years of age and older was evaluated in Study 4 (NCT02842866). The safety analysis set included 448 participants who received MenQuadfi intramuscularly and 453 participants who received a non-conjugate comparator meningococcal vaccine, Menomune® – A/C/Y/W-135 [Meningococcal Polysaccharide Vaccine, Groups A, C, Y, and W-135 Combined], subcutaneously. Of the participants 56 years of age and older who received MenQuadfi (N = 448), 44.4% were 56 through 64 years of age, 55.6% were 65 years of age and older, 57.6% were female, 86.6% were White, 11.6% were Black or African American, 1.1% were Asian, 0.4% were of other racial groups and 7.8% were of Hispanic or Latino ethnicity. Mean age was 67.0 years at time of administration.

The rates and severity of the solicited adverse reactions that occurred within 7 days following MenQuadfi compared with Menomune in Study 4 (NCT02842866) are presented in Table 4.

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 4: Percentages of Solicited Injection-Site Reactions and Systemic Adverse Reactions within 7 Days after Vaccination with MenQuadfi or Menomune in Individuals 56 Years of Age and Older Study 4*

	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

	MenQuadfi (N†=436-443) %		Menomune‡ (N†=449-451) %	
Adverse Reactions	Any	Grade 3	Any	Grade 3
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

* Clinical trial identifier NCT02842866
† 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)

Booster Vaccination Study

The safety of MenQuadfi in previously vaccinated adolescents and adults 15 years of age and older was evaluated in Study 5 (NCT02752906). All randomized participants had received a primary dose of either (Menveo or Menactra) 4 to 10 years previously. The safety analysis set included 402 participants who received a single booster dose of MenQuadfi (median age: 17.8 years) and 407 participants who received a single booster dose of Menactra (median age: 17.9 years). Of the participants who received MenQuadfi, 51.5% were female, 85.1% were White, 9.7% were Black, 2.7 % were Asian and 2.2 % were of other racial groups, and 15.7% were of Hispanic or Latino ethnicity.

The most commonly reported solicited adverse reactions (≥10%) within 7 days of MenQuadfi booster vaccination were injection site pain (44.7%) and headache (37.9%), myalgia (36.7%), and malaise (27.6%). The majority of solicited adverse reactions were Grade 1 or 2 and resolved within 3 days. Compared with recipients of a Menactra booster dose, recipients of a MenQuadfi booster dose had higher rates of injection site erythema (MenQuadfi 5.0%, Menactra 1.5%) and swelling (MenQuadfi 4.0%, Menactra 0.7%). Overall rates of solicited adverse reactions were comparable to those observed in unvaccinated adolescents and adults after a single MenQuadfi dose.

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.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

In a clinical trial in adolescents 10 through 17 years of age, MenQuadfi was administered concomitantly with Tdap and HPV [*see Adverse Reactions (6)* and *Clinical Studies (14.3)*].

Lower geometric mean antibody concentrations (GMCs) for antibodies to the pertussis antigens filamentous hemagglutinin (FHA), pertactin (PRN) and fimbriae (FIM) were observed when MenQuadfi was co-administered with Tdap and HPV, compared to concomitant administration of Tdap and HPV (without MenQuadfi) [*see Clinical Studies (14.3)*].

7.2 Immunosuppressive Treatments

Immunosuppressive therapies may reduce the immune response to MenQuadfi [*see Warnings and Precautions (5)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to MenQuadfi during pregnancy. To enroll in or obtain information about the registry, call Sanofi Pasteur at 1-800-822-2463.

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

There are no clinical studies of MenQuadfi in pregnant women. Available human data on MenQuadfi administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

A developmental toxicity study in female rabbits administered a full human dose (0.5 mL) prior to mating and during gestation period revealed no evidence of harm to the fetus due to MenQuadfi (see *Animal Data*).

Data

Animal Data

In a developmental toxicity study, female rabbits received a human dose of MenQuadfi by intramuscular injection on five occasions: 30 days and 10 days prior to mating, gestation days 6, 12 and 27. No adverse effects on pre-weaning development up to post-natal day 35 were observed. There were no vaccine-related fetal malformations or variations observed.

8.2 Lactation

Risk Summary

It is not known whether MenQuadfi is excreted in human milk. Data are not available to assess the effects of MenQuadfi on the breastfed infant or on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MenQuadfi and any potential adverse effects on the breastfed child from MenQuadfi or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of MenQuadfi have not been established in individuals younger than 2 years of age in the US.

8.5 Geriatric Use

A total of 249 participants 65 years of age and older, including 71 participants 75 years of age or older, in Study 4 received one dose of MenQuadfi [*see Adverse Reactions (6.1)* and *Clinical Studies (14.1)*].

MenQuadfi recipients ≥ 65 years of age had lower GMTs and seroresponse rates for all serogroups compared to MenQuadfi recipients 56 through 64 years of age [*see Clinical Studies (14.1)*].

11 DESCRIPTION

MenQuadfi is a sterile liquid vaccine administered by intramuscular injection that contains *Neisseria meningitidis* serogroup A, C, W, and Y capsular polysaccharide antigens that are 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 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). The activated/derivatized polysaccharides are covalently linked to tetanus toxoid and purified by chromatography and serial diafiltration. The four meningococcal components, present as individual serogroup-specific glycoconjugates, compose the final formulated vaccine.

MenQuadfi is manufactured as a sterile, clear, colorless solution. Each 0.5 mL dose of vaccine contains 10 microgram each of meningococcal A, C, W, and Y polysaccharide antigens conjugated to approximately 55 micrograms tetanus toxoid protein carrier; 3.35 mg sodium chloride (0.67%), and 1.23 mg sodium acetate (30 mM). Potency of MenQuadfi is determined by quantifying the amount of each polysaccharide antigen that is conjugated to tetanus toxoid protein and the amount of unconjugated polysaccharide present.

No preservative or adjuvant is added during manufacture. Each 0.5 mL dose may contain residual amounts of formaldehyde of less than 3 mcg/mL, by calculation.

The vial in which the vaccine components are contained is composed of USP Type I borosilicate glass. The vial stopper is a chlorobutyl synthetic polyisoprene blend stopper (not made with natural rubber latex).

12 CLINICAL PHARMACOLOGY

12.1 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 in serum 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

MenQuadfi has not been evaluated for carcinogenic or mutagenic potential or for impairment of male fertility. MenQuadfi administered to female rabbits had no effects on fertility [*see Use in Specific Population (8.1)*].

14 CLINICAL STUDIES

To infer effectiveness of MenQuadfi, the immunogenicity in persons 2 years of age and older was evaluated using a serogroup-specific serum bactericidal assay with exogenous human complement (hSBA). The hSBA responses following a single dose of MenQuadfi for primary vaccination were assessed in four studies, and the hSBA responses following a single dose of MenQuadfi for booster vaccination were assessed in one study. Serum was collected at baseline and 30 days post-vaccination to measure antibodies with hSBA. The hSBA geometric mean titers (GMTs) and proportion of participants who achieved hSBA seroresponse (defined below) were evaluated.

- Seroresponse rate 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.

Non-inferiority of MenQuadfi seroresponse rates versus those for comparator vaccines was demonstrated for all 4 serogroups in individuals 2 years of age and older who received a primary vaccination and in individuals 15 years of age and older who received a booster vaccination at least 4 years following a previous dose of a meningococcal (groups A, C, W, Y) conjugate vaccine.

14.1 Primary Vaccination

Immunogenicity in Children 2 through 9 Years of Age

Immunogenicity of MenQuadfi compared to Menveo in participants 2 through 9 years of age was evaluated in Study 1 (NCT03077438). The hSBA seroresponse rate and GMTs are presented in Table 5.

Immune non-inferiority, based on seroresponse rates, was demonstrated for MenQuadfi as compared to Menveo for all four serogroups.

Table 5: Comparison of Bactericidal Antibody Responses to MenQuadfi and Menveo 30 Days after Vaccination of Participants 2 through 9 Years of Age (Study 1)*

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)
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)
GMT	238 (209; 270)	17.0 (14; 20)	
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)
GMT	38 (34; 42)	26 (23; 30)	

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)
GMT	69 (61; 77)	44 (38; 50)	

* Clinical trial identifier NCT03077438

† Seroresponse rate (primary endpoint) 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.

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 Adolescents 10 through 17 Years of Age

Immunogenicity of MenQuadfi compared to Menveo in participants 10 through 17 years of age was evaluated in Study 2 (NCT02199691). Study 2 was conducted in healthy meningococcal vaccine naïve participants and evaluated seroresponse rates following administration with either MenQuadfi alone, Menveo alone, MenQuadfi co-administered with Tdap, and HPV, or Tdap and HPV alone. The hSBA seroresponse rate and GMTs for Study 2 are presented in Table 6.

Immune non-inferiority, based on seroresponse, was demonstrated for MenQuadfi as compared to Menveo for all four serogroups.

Study 2 (NCT02199691) was conducted in healthy meningococcal vaccine naïve male and female participants and evaluated seroresponses following administration with either MenQuadfi alone; Menveo alone; MenQuadfi co-administered with Tdap, and HPV; or Tdap and HPV alone. The hSBA seroresponse rate and GMTs for the MenQuadfi alone and Menveo alone groups are presented in Table 6.

Table 6: Comparison of Bactericidal Antibody Responses to MenQuadfi and Menveo 30 Days after Vaccination of Participants 10 through 17 Years of Age Study 2*

Endpoint†	MenQuadfi (95% CI)	Menveo (95% CI)	Percent difference MenQuadfi minus Menveo‡ (95% CI)
A	N=463	N=464	
% Participants achieving Seroresponse	70.2 (65.8; 74.3)	60.3 (55.7; 64.8)	9.8 (3.7;15.9)

Endpoint†	MenQuadfi (95% CI)	Menveo (95% CI)	Percent difference MenQuadfi minus Menveo‡ (95% CI)
GMT	44 (39; 50)	35 (30; 41)	
C	N=462	N=463	
% Participants achieving Seroresponse	96.1 (93.9, 97.7)	61.6 (57.0, 66.0)	34.5 (29.7; 39.3)
GMT	387 (329; 456)	51 (41; 64)	
W	N=463	N=464	
% Participants achieving Seroresponse	84.2 (80.6; 87.4)	56.0 (51.4; 60.6)	28.2 (22.5; 33.7)
GMT	87 (78; 97)	36 (32; 41)	
Y	N=462-463	N=464	
% Participants achieving Seroresponse	91.1 (88.2; 93.6)	66.8 (62.3;71.1)	24.3 (19.2; 29.3)
GMT	76 (66; 87)	28 (24; 32)	

* Clinical trial identifier NCT02199691

† Seroresponse rate (primary endpoint) 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.

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.

Study 3 evaluated the immunogenicity of MenQuadfi (N=1097-1098) compared to Menactra (N=300) in healthy meningococcal-naïve participants 10 through 17 years of age. Seroresponse rates for MenQuadfi were noninferior to those of Menactra for all serogroups based on the same noninferiority criteria defined for Study 2.

Immunogenicity in Adults 18 through 55 Years of Age

Immunogenicity of MenQuadfi compared to Menactra in participants 18 through 55 years of age was evaluated in Study 3 (NCT02842853). The hSBA seroresponse rate and GMTs are presented in Table 7.

Immune non-inferiority, based on seroresponse rates, was demonstrated for MenQuadfi as compared to Menactra for all four serogroups.

Table 7: Comparison of Bactericidal Antibody Responses to MenQuadfi and Menactra 30 Days after Vaccination of Participants 18 through 55 Years of Age Study 3*

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)
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)
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)
GMT	76 (69; 83)	33 (26; 42)	

Endpoint†	MenQuadfi (95% CI)	Menactra (95% CI)	Percent difference MenQuadfi minus Menactra‡ (95% CI)
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)
GMT	219 (200; 239)	55 (42; 70)	

* Clinical trial identifier NCT02842853

† Seroresponse rate (primary endpoint) 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 in Adults 56 Years of Age and Older

Immunogenicity of MenQuadfi compared to Menomune in participants 56 years and older was evaluated in Study 4 (NCT02842866).

Enrollment was stratified by age category: 56 through 64 years of age (44.3%), 65 through 74 years of age (39.7%), and 75 years of age and older (15.9%). The overall mean age of participants who received MenQuadfi was 66.9 years; range: 56 through 89.8 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 8.

Immune non-inferiority, based on seroresponse rates, was demonstrated for MenQuadfi as compared to Menomune for all four serogroups.

Table 8: Comparison of Bactericidal Antibody Responses to MenQuadfi and Menomune in Naïve Older Adults and Elderly 30 Days after Vaccination Study 4*

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)
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)
GMT	101 (84; 123)	25 (21; 30)	
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)
GMT	28 (24; 33)	15 (13; 18)	
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)
GMT	69 (59; 81)	21 (17; 25)	

*Clinical trial identifier NCT02842866

† Seroresponse rate (primary endpoint) 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.

14.2 Booster

Immunogenicity of a booster dose of MenQuadfi compared to a booster dose of Menactra was evaluated in Study 5 (NCT02752906). The study-enrolled participants 15 years of age and older who had received a primary dose of Menveo or Menactra 4 to 10 years previously.

Immune non-inferiority, based on seroresponse rates, was demonstrated for MenQuadfi as compared to Menactra for all four serogroups.

For a description of study design and number of participants, see section 6.1 Booster Vaccination Study. The primary immunogenicity endpoint was hSBA seroresponse to each serogroup 30 days following booster vaccination with MenQuadfi or Menactra given to participants who received a prior dose of Menveo or Menactra 4 to 10 years ago. Seroresponse was defined as 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 other endpoints included the proportions of participants with post-vaccination hSBA ≥1:8 and the hSBA GMTs for each serogroup. These endpoints were also evaluated at 6 days post vaccination in a subset.

Seroresponse rates at Day 30 following booster vaccination with MenQuadfi were 92.2% for serogroup A, 97.1% for serogroup C, 98.2% for serogroup W, and 97.4% for serogroup Y, as compared to 87.1% for serogroup A, 91.8% for serogroup C, 90.7% for serogroup W, and 95.6% for serogroup Y, following booster vaccination with Menactra. At Day 6, following booster vaccination with MenQuadfi, seroresponse rates were 72.7%, 83.6%, 94.5%, and 90.9% for serogroups A, C, W, and Y, respectively.

The hSBA GMTs were 173, 334, 499, and 302 for serogroups A, C, W, and Y at Day 6, and 497, 2618, 1747, and 2070, respectively, for the 4 serogroups at Day 30 following booster dose of MenQuadfi.

Overall, similar seroresponse rates were observed for those participants who received booster vaccination with Menactra.

14.3 Immunogenicity of Concomitantly Administered Vaccines

Concomitant administration of MenQuadfi with Tdap and HPV in adolescents 10 through 17 years was evaluated in Study 2 (NCT02199691). In this randomized study, 503 participants received MenQuadfi alone, 392 received MenQuadfi coadministered with Tdap and HPV, 296 received Tdap and HPV alone. A fourth group received Menveo alone (N=501).

No evidence of interference in hSBA seroresponse rates was observed when MenQuadfi was coadministered with Tdap and HPV. Antibody responses to HPV, and to the tetanus and diphtheria antigens were similar when Tdap and HPV were administered with and without MenQuadfi. Anti-pertussis GMC responses were non-inferior for the pertussis toxoid antigen, but did not meet non-inferiority for the FHA, PRN, and FIM antigens. The clinical relevance of the diminished responses to the pertussis antigens is unknown.

16 HOW SUPPLIED/STORAGE AND HANDLING

MenQuadfi is supplied in a single-dose vial (NDC 49281-590-58), in packages of 5 vials (NDC 49281-590-05).

The vial stopper is not made with natural rubber latex.

Store at 2°C to 8°C (35°F to 46°F). Do not freeze. Do not use vaccine that has been frozen. Do not use after expiration date.

17 PATIENT COUNSELING INFORMATION

Vaccine Information Statements are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization to the patient, parent, or guardian. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines). Inform the patients, parents or guardians about:

- Potential benefits and risks of immunization with MenQuadfi.
- Potential for adverse reactions that have been temporally associated with administration of MenQuadfi or other vaccines containing similar components.
- Reporting any adverse reactions to their healthcare provider.
- The Sanofi Pasteur Inc. Pregnancy Registry, as appropriate [*see Pregnancy (8.1)*].

Manufactured by:
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