WHO Product Information

1. NAME OF THE MEDICINAL PRODUCT

MenQuadfi solution for injection
Meningococcal Group A, C, W and Y conjugate vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 mL) contains:
Neisseria meningitidis group A polysaccharide[1] .....10 micrograms
Neisseria meningitidis group C polysaccharide[1].....10 micrograms
Neisseria meningitidis group Y polysaccharide[1] .....10 micrograms
Neisseria meningitidis group W polysaccharide[1] .....10 micrograms
[1]Conjugated to tetanus toxoid carrier protein.....55 micrograms

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

The use of this vaccine should be in accordance with available official recommendations.

4.2 Posology and method of administration

Posology

Primary vaccination:
- Individuals 12 months of age and older: One single dose (0.5 mL).

Booster vaccination:
- A single 0.5 mL dose of MenQuadfi may be used to boost subjects who have previously received a meningococcal vaccine containing the same serogroups (see section 5.1).
- There are no data available to indicate the need for or timing of a booster dose of MenQuadfi (see section 5.1).

Other paediatric population
The safety and immunogenicity of MenQuadfi in individuals under 12 months of age have not yet been established.

Method of administration
For intramuscular injection only, preferably in the deltoid region or anterolateral thigh depending on the recipient's age and muscle mass.

For instructions on handling of the vaccine before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 or after previous administration of the vaccine or a vaccine containing the same components.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

MenQuadfi should not be administered subcutaneously, intravascularly or intradermally.

It is good clinical practice to precede vaccination by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable effects) and a clinical examination.

Hypersensitivity
As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following administration of the vaccine.

Intercurrent illness
Vaccination should be postponed in individuals suffering from an acute severe febrile illness. However, the presence of a minor infection, such as cold, should not result in the deferral of vaccination.

Syncope
Syncope (fainting) and other anxiety-related reactions can occur following or even before any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent falling or injury and to manage syncope.

Thrombocytopenia and coagulation disorders
MenQuadfi should be given with caution to individuals with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection, unless the potential benefit clearly outweighs the risk of administration.

Protection
MenQuadfi will only protect against *Neisseria meningitidis* groups A, C, W, and Y. The vaccine will not protect against any other *Neisseria meningitidis* groups.

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

Waning of serum bactericidal antibody titres against serogroup A when using human complement in the assay (hSBA) has been reported for other quadrivalent meningococcal vaccines. The clinical relevance of this observation is unknown. No data are available for MenQuadfi.

Lower hSBA geometric mean titres (GMTs) against serogroup A have been observed after a single dose of MenQuadfi was administered to toddlers who previously received serogroup C meningococcal conjugate vaccine (MenC-CRM) during infancy. Nevertheless, seroprotection rates were comparable between treatment groups (see section 5.1). The clinical relevance of this observation is unknown. This aspect might be considered for individuals at high risk for MenA infection who received MenC-CRM vaccine in their first year of life.

Immunodeficiency
It may be expected that in patients receiving immunosuppressive treatment or patients with immunodeficiency, an adequate immune response may not be elicited (see section 4.5). Persons with familial complement deficiencies (for example, C5 or C3 deficiencies) and persons receiving treatments that inhibit terminal complement activation (for example, eculizumab) are at increased risk of invasive disease caused by *Neisseria meningitidis* groups A, C, W, and Y, even if they develop antibodies following vaccination with MenQuadfi. No data on immunocompromised patients are available.

Tetanus immunisation
Immunisation with MenQuadfi vaccine does not substitute for routine tetanus immunisation. Co-administration of MenQuadfi with a tetanus toxoid-containing vaccine does not impair the response to tetanus toxoid or impact the safety.

Sodium content
This medicine contains less than 1 mmol sodium (23 mg) per dose that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Use with other vaccines
Injection sites on separate limbs and separate syringes must be used in the case of concomitant administration.

For ages 12-23 months, MenQuadfi can be co-administered with the measles-mumps-rubella vaccine (MMR) and varicella vaccine (V), combined diphtheria - tetanus - acellular pertussis (DTaP) vaccines, including combination DTaP vaccines with hepatitis B (HBV), inactivated poliovirus (IPV) or *Haemophilus influenzae* type b (Hib) such as DTaP-IPV-HB-Hib (Hib conjugated to tetanus toxoid) vaccine and 13-valent pneumococcal polysaccharide conjugated vaccine (PCV-13).

For ages 10-17 years, MenQuadfi can be co-administered with diphtheria, tetanus, pertussis (acellular, component) vaccine (adsorbed, reduced antigen(s) content) (Tdap) and human papillomavirus vaccine (recombinant, adsorbed) (HPV).

MenQuadfi can be administered concomitantly with PCV-13. Lower hSBA GMTs on day 30 post-dose for serogroup A has been observed when given concommitantly. The clinical relevance of this observation is unknown. As a precaution in children 12-23 months of age at high risk for serogroup A disease, consideration might be given for administration of MenQuadfi and PCV-13 vaccines separately.

Meningococcal vaccine naïve children aged 10-17 years had non inferior response for PT and lower antibody responses to FHA, PRN and FIM when Tdap vaccine was administered concomitantly with MenQuadfi and HPV compared to co-administration with HPV vaccine alone. The clinical implications of the observed pertussis antigen responses also observed with the existing quadrivalent meningococcal conjugate vaccines are unknown.

Concomitant vaccines should always be administered at separate injection sites and preferably contralateral.

Concomitant administration of MenQuadfi and other vaccines than those listed above has not been studied.

Use with systemic immunosuppressive medicinal products
It may be expected that in patients receiving immunosuppressive treatment an adequate immune response may not be elicited (see also section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There is limited amount of data on the use of MenQuadfi in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). MenQuadfi should be used during pregnancy only if the expected benefits for the mother outweigh the potential risks, including those for the foetus.

Breast-feeding
It is unknown whether MenQuadfi is excreted in human milk. MenQuadfi should only be used during breast-feeding when the possible advantages outweigh the potential risks.

Fertility
A developmental and reproductive toxicity study was performed in female rabbits. There were no effects on mating performances or female fertility. No study was conducted on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

MenQuadfi has no or negligible influence on the ability to drive and use machines.

However, some of the effects mentioned under section 4.8 “Undesirable effects” may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of a single dose of MenQuadfi in individuals 12 months of age and older was evaluated in seven randomized, active-controlled, multi-centre pivotal studies. In these studies, 6,308 subjects received either a primary dose (N=5,906) or a booster dose (N=402) of MenQuadfi and were included in the safety analyses. This included 1,389 toddlers aged 12 through 23 months of age, 498 children aged 2 through 9 years, 2,289 adolescents aged 10 through 17 years, 1,684 adults aged 18 through 55 years, 199 older adults aged 56 through 64 years, and 249 elderly aged 65 years and older. Of these, 392 adolescents received MenQuadfi co-administered with Tdap and HPV, and 589 toddlers received MenQuadfi co-administered with MMR+V (N=189), DTaP-IPV-HB-Hib (N=200) or PCV-13 (N=200).

The most frequently reported adverse reactions within 7 days after vaccination with a single dose of MenQuadfi alone in toddlers 12 through 23 months of age were irritability (36.7%) and injection site tenderness (30.6%) and in ages 2 years and above were injection site pain (38.7%) and myalgia (30.5%). These adverse reactions were mostly mild or moderate in intensity.
Rates of adverse reactions after a booster dose of MenQuadfi in adolescents and adults at least 15 years of age were comparable to those seen in adolescents and adults who received a primary dose of MenQuadfi.

Rates of adverse reactions within 7 days following vaccination among toddlers were comparable when MMR+V were given concomitantly with or without MenQuadfi, and when DTaP-IPV-HB-Hib was given with or without MenQuadfi. Overall, the rates of adverse reactions were higher in toddlers who received PCV-13 given concomitantly with MenQuadfi (36.5%) than in toddlers who received PCV-13 alone (17.2%).

Tabulated list of adverse reactions

The following adverse reactions, as listed below, have been identified from clinical studies conducted with MenQuadfi when given alone to subjects 2 years of age and older. The safety profile observed in toddlers aged 12 through 23 months is presented in the paediatric population section.

The adverse reactions are listed according to the following frequency categories:
Very common (≥1/10);
Common (≥1/100 to <1/10);
Uncommon (≥1/1,000 to <1/100);
Rare (≥1/10,000 to <1/1,000).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Tabulated summary of adverse reactions following administration of MenQuadfi from clinical trials in subjects 2 years of age and above

MedDRA System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Rare	Lymphadenopathy
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness
Gastrointestinal disorders	Uncommon	Vomiting, nausea
	Rare	Diarrhoea, stomach pain
Skin and subcutaneous tissue disorders	Rare	Urticaria, pruritus, rash
Musculoskeletal and connective tissue disorders	Very common	Myalgia
	Rare	Pain in extremity
General disorders and administration site conditions	Very common	Malaise
		Injection site pain
	Common	Fever
		At the injection site: swelling, erythema
	Uncommon	Fatigue
		At the injection site: pruritus, warmth, bruising, rash
	Rare	Chills, axillary pain
		At the injection site: induration

Paediatric population

The safety profile of MenQuadfi in children and adolescents 2 through 17 years of age was generally comparable to that in adults. Injection site erythema and swelling at the MenQuadfi injection site were reported more frequently in children 2 through 9 years of age (very common) than in the older age groups.

In toddlers 12 through 23 months of age, injection site erythema and swelling (very common) at the MenQuadfi injection site, vomiting (common) and diarrhoea (common), were reported more frequently than in the older age groups. The following additional reactions, as listed below in Table 2, have been reported very commonly or commonly following administration of MenQuadfi in toddlers during clinical trials:

Table 2: Tabulated summary of adverse reactions following administration of MenQuadfi from clinical trials in subjects 12 months through 23 months

MedDRA System Organ Class	Frequency	Adverse reactions
Metabolic and nutrition disorders	Very common	Appetite lost
Psychiatric disorders	Very common	Irritability
	Uncommon	Insomnia
Nervous system disorders	Very common	Drowsiness
Gastrointestinal disorders	Common	Vomiting, diarrhoea
Skin and subcutaneous tissue disorders	Uncommon	Urticaria

MedDRA System Organ Class	Frequency	Adverse reactions
General disorders and administration site conditions	Very Common	Abnormal crying
		At the injection site: tenderness/pain, erythema, swelling
	Common	Fever
	Uncommon	At the injection site: pruritus, induration, bruising, rash

Older population
Overall, within 7 days after vaccination with a single dose of MenQuadfi, the same injection site and systemic adverse reactions were observed in older (≥56 years of age) and younger adults (18 through 55 years old) but at lower frequencies; except for injection site pruritus, which was more frequent (common) in older adults. These adverse reactions mostly were mild or moderate in intensity.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

Overdose with MenQuadfi is unlikely due to its presentation as a single dose vial. In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended..

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: meningococcal vaccines

ATC code: J07AH08

Mechanism of action
Anti-capsular meningococcal antibodies protect against meningococcal diseases via complement mediated bactericidal activity.
MenQuadfi induces the production of bactericidal antibodies specific to the capsular polysaccharides of *Neisseria meningitidis* serogroups A, C, W, and Y.

Immunogenicity
The immunogenicity of a single dose of MenQuadfi for primary vaccination in toddlers (12-23 months of age), children and adolescents (2-17 years of age), adults (18-55 years of age) and older adults (56 years and above) was assessed in six pivotal studies and in one post licensure supportive study in toddlers (12-23 months of age). The immunogenicity of a single dose of MenQuadfi for booster vaccination (subjects 15 to 55 years of age) was assessed in one pivotal study. In addition, antibody persistence after primary vaccination and immunogenicity of a booster dose was assessed in one post licensure supportive study in children (4-5 years of age).

Primary immunogenicity analyses were conducted by measuring serum bactericidal activity (SBA) using human serum as the source of exogenous complement (hSBA). Rabbit complement (rSBA) data are available in subsets in all age groups and generally follows the trends observed with human complement (hSBA) data. In addition, all subjects were assessed for primary immunogenicity measured by hSBA and rSBA for serogroup C in MEQ00065 study [NCT03890367].

Clinical data on the persistence of antibody response 3 years after primary vaccination with MenQuadfi at 12-23 months of age are available in children 4-5 years of age. Clinical data on booster vaccination with MenQuadfi in those children are also available.

Toddlers 12 to 23 month of age

Immunogenicity in subjects 12 through 23 months of age was evaluated in two clinical studies (MET51 [NCT02955797], MET57 [NCT03205371]) and MEQ00065 [NCT03890367]).

MET51 was conducted in subjects who were either meningococcal vaccine naïve or had been primed with monovalent meningococcal C conjugate vaccines in their first year of life (see Table 3).

Table 3: Comparison of bactericidal antibody responses to MenQuadfi and MenACWY-TT vaccine 30 days after vaccination of meningococcal vaccine naïve subjects only or combined (naïve + MenC primed) subjects 12 through 23 months of age (study MET51*)

Endpoint by Serogroup	MenQuadfi (95% CI) Naïve	MenACWY-TT (95% CI) Naïve	MenQuadfi (95% CI) Combined (Naïve + MenC Primed)	MenACWY-TT (95% CI) Combined (Naïve + MenC Primed)
A	N=293	N=295	N=490	N=393-394
% ≥1:8 (Seroprotection)**	90.8 (86.9; 93.8)	89.5 (85.4; 92.7)	90.4 (87.4; 92.9)	91.6 (88.4; 94.2)
% Seroresponse	76.8 (71.5; 81.5)	72.5 (67.1; 77.6)	76.5 (72.5; 80.2)	77.1 (72.6; 81.2)
hSBA GMT	28.7 (25.2; 32.6)	28.0 (24.4; 32.1)	29.9 (26.9; 33.2)	34.5 (30.5; 39.0)
C	N=293	N=295	N=489	N=393-394
% ≥1:8 (Seroprotection)**	99.3 (97.6; 99.9)	81.4 (76.4; 85.6)	99.2 (97.9; 99.8)	85.5 (81.7; 88.9)
% Seroresponse	98.3 (96.1; 99.4)	71.5 (66.0; 76.6)	97.1 (95.2; 98.4)	77.4 (72.9; 81.4)
hSBA GMT	436 (380; 500)	26.4 (22.5; 31.0)	880 (748; 1035)	77.1 (60.7; 98.0)
W	N=293	N=296	N=489	N=393-394
% ≥1:8 (Seroprotection)**	83.6 (78.9; 87.7)	83.4 (78.7; 87.5)	84.9 (81.4; 87.9)	84.0 (80.0; 87.5)
% Seroresponse	67.6 (61.9; 72.9)	66.6 (60.9; 71.9)	70.8 (66.5; 74.8)	68.4 (63.6; 73.0)
hSBA GMT	22.0 (18.9; 25.5)	16.4 (14.4; 18.6)	24.4 (21.8; 27.5)	17.7 (15.8; 19.8)
Y	N=293	N=296	N=488-490	N=394-395
% ≥1:8 (Seroprotection)**	93.2 (89.7; 95.8)	91.6 (87.8; 94.5)	94.3 (91.8; 96.2)	91.6 (88.5; 94.2)
% Seroresponse	81.9 (77.0; 86.1)	79.1 (74.0; 83.5)	84.8 (81.3; 87.9)	78.9 (74.6; 82.9)
hSBA GMT	38.0 (33.0; 43.9)	32.2 (28.0; 37.0)	41.7 (37.5; 46.5)	31.9 (28.4; 36.0)

* Clinical trial identifier NCT02955797
N: number of subjects in the per-protocol analysis set with valid serology results.
95% CI of the single proportion calculated from the exact binomial method.
** Non-inferiority criterion met

Response in subjects previously vaccinated with MenC conjugate vaccines in their first year of life:
The majority of monovalent meningococcal C conjugate vaccine primed toddlers (12-23 months of age) in study MET51 (NCT02955797) had hSBA titres ≥1:8 in the MenQuadfi group (N=198) (≥ 86.7%) and in MenACWY-TT group (N=99) (≥ 85.7%) at D30 post-vaccination. These toddlers received during their infancy MenC-TT or MenC-CRM vaccines. Post-vaccination seroprotection rates were comparable between MenQuadfi and MenACWY-TT for all serogroups regardless of the priming background.

In MenC-CRM primed subjects the GMTs for serogroup A were lower in the MenQuadfi group (n=49) than in the MenACWY-TT group (n=25) [12.0 (8.23; 17.5) vs 42.2 (25.9; 68.8)]. After administration of Menquadfi seroprotection rates (hSBA titres ≥1:8) for subjects primed with MenC-CRM were lower but still comparable for serogroups A and W compared with those in the MenACWY-TT group [A: 68.8% (53.7; 81.3) vs 96.0% (79.6; 99.9); W: 68.1% (52.9; 80.9) vs 79.2% (57.8; 92.9)]. The rates of serogroup Y were higher but still comparable with those in the MenACWY-TT group [95.8% (85.7; 99.5) vs 80.0% (59.3; 93.2)]. The rates for serogroup C were comparable in both groups [95.7% (85.5; 99.5) vs 92.0% (74.0; 99.0)]. The clinical relevance of these results is unknown. This aspect might be considered for individuals at high risk for MenA infection who received MenC-CRM vaccine in their first year of life.

MET57 (NCT03205371) was conducted in meningococcal vaccine naïve toddlers 12 through 23 months of age to assess the immunogenicity of the concomitant administration of MenQuadfi with paediatric vaccines (MMR+V, DTaP-IPV-HB-Hib or PCV-13). Overall, the post-vaccination hSBA seroprotection rates in subjects who received MenQuadfi was high for all serogroups (between 88.9% and 100%). Seroresponse and seroprotection rates for serogroup A were comparable when MenQuadfi was co-administered with PCV-13 and alone (56.1%, [95% CI 48.9; 63.2] and 83.7% [95% CI 77.7; 88.6] vs 71.9% [95%CI 61.8; 80.6] and 90.6% [95%CI 82.9; 95.6]). There were differences in the hSBA GMTs for serogroup A when MenQuadfi was co-administered with PCV-13 (n=196) compared with MenQuadfi administered alone (n=96) (24.6 [95%CI 20.2; 30.1] and 49.0 [95%CI 36.8; 65.3]). The clinical relevance of these results is unknown but this observation might be taken into consideration for individuals at high risk for MenA infection and consequently vaccinations with MenQuadfi and PCV13 might be performed separately.

MEQ00065 (NCT03890367) study was conducted in meningococcal vaccine naïve toddlers 12 through 23 months of age to assess the immunogenicity of serogroup C using hSBA and rSBA assays following administration of a single dose of MenQuadfi compared to MenACWY-TT or to MenC-TT.

Superiority of MenQuadfi was demonstrated in comparison to MenACWY-TT vaccine for the hSBA seroprotection rate and hSBA and rSBA GMTs to meningococcal serogroup C. Non-inferiority was demonstrated for the rSBA seroprotection rate to meningococcal serogroup C.

Superiority of MenQuadfi was also demonstrated in comparison to MenC-TT vaccine for the rSBA and hSBA GMTs to meningococcal serogroup C and non-inferiority was demonstrated for the rSBA and hSBA seroprotection rates to meningococcal serogroup C (see Table 4).

Table 4: Comparison of hSBA and rSBA bactericidal antibody responses for serogroup C to MenQuadfi, MenACWY-TT and MenC-TT vaccines 30 days after vaccination of meningococcal vaccine naïve subjects 12 through 23 months of age (study MEQ00065*)

Endpoints	MenQuadfi (95% CI)	MenACWY-TT (95% CI)	MenC-TT (95% CI)	MenQuadfi (95% CI)	MenACWY-TT (95% CI)	MenC-TT (95% CI)
	hSBA			rSBA		
	N=214	N=211	N= 216	N=213	N=210	N= 215
% ≥1:8 (Seroprotection)	99.5[#§] (97.4; 100)	89.1 (84.1; 93.0)	99.5 (97.4; 100)	100[¶] (98.3; 100)	94.8 (90.8; 97.4)	100 (98.3; 100)
% Seroresponse	99.5 (97.4; 100)	83.4 (77.7; 88.2)	99.1 (96.7; 99.9)	99.5 (97.4; 100)	92.9 (88.5; 95.9)	99.5 (97.4; 100)
GMTs	515[$] (450; 591)	31,6 (26.5; 37.6)	227 (198; 260)	2143[¥] (1870; 2456)	315 (252; 395)	1624 (1425; 1850)

* Clinical trial identifier NCT03890367
# superiority of MenQuadfi demonstrated versus MenACWY-TT (hSBA seroprotection rates)
§ non inferiority of MenQuadfi demonstrated versus MenC-TT (hSBA seroprotection rates)
$ superiority of MenQuadfi demonstrated versus MenACWY-TT and MenC-TT (hSBA GMTs)
¶ non inferiority of MenQuadfi demonstrated versus MenACWY-TT and MenC-TT (rSBA seroprotection rates)
¥ superiority of MenQuadfi demonstrated versus MenACWY-TT and MenC-TT (rSBA GMTs)
N = number of subjects in the per-protocol analysis set with valid serology results
95% CI of the single proportion calculated from the exact binomial method

Immunogenicity booster and persistence response

MET62 (NCT03476135) evaluated the antibody persistence of a primary dose, immunogenicity and the safety of a booster dose of MenQuadfi in children 4-5 years of age. These children were primed with a single dose of MenQuadfi or MenACWY-TT 3 years before as part of the phase II study MET54 when they were 12-23 months old. The antibody persistence prior to the MenQuadfi booster dose and the booster immune response were assessed according to the vaccine (MenQuadfi or MenACWY-TT) children had received 3 years ago (see Table 5).

For all serogroups, hSBA GMTs were higher at D30 post-primary dose than at D0 pre-booster dose for MenQuadfi or MenACWY-TT. The pre-booster GMTs were higher than the pre-primary dose, indicative of long-term persistence of immune response.

After the booster dose, seroprotection rates were nearly 100% for all serogroups in children primed with MenQuadfi.

Table 5: Comparison of bactericidal antibody response 30 days after booster vaccination, and persistence in children (4-5 years) primed with MenQuadfi or MenACWY-TT 3 years before in study MET54* – (study MET62)**

Serogroup by Endpoint	MenQuadfi Booster in MenQuadfi primed (95% CI)			MenQuadfi Booster in MenACWY-TT primed (95% CI)			MenQuadfi Booster in MenQuadfi primed + MenACWY-TT primed (95% CI)		
	Persistence[#] N=42		Booster[$] N=40	Persistence[#] N=49		Booster[$] N=44	Persistence[#] N=91		Booster[$] N=84
	D30 Post primary dose	D0-Pre-booster dose		D30 Post primary dose	D0-Pre-booster dose		D30 Post primary dose	D0-Pre-booster dose	
A									
% ≥1:8 (Seroprotection)	97.6 (87.4; 99.9)	66.7 (50.5; 80.4)	100 (91.2; 100)	89.8 (77.8; 96.6)	83.7 (70.3; 92.7)	100 (92.0; 100)	93.4 (86.2; 97.5)	75.8 (65.7; 84.2)	100 (95.7; 100)
% Seroresponse	-	-	100 (91.2; 100)	-	-	95.5 (84.5; 99.4)	-	-	97.6 (91.7; 99.7)
hSBA GMT	83.3 (63.9; 109)	11.9 (8.11; 17.4)	763 (521; 1117)	49.6 (32.1; 76.7)	14.7 (10.7; 20.2)	659 (427; 1017)	63.0 (48.3; 82.2)	13.3 (10.5; 17.0)	706 (531; 940)
C									
% ≥1:8 (Seroprotection)	100 (91.6; 100)	100 (91.6; 100)	100 (91.2; 100)	87.8 (75.2; 95.4)	57.1 (42.2; 71.2)	100 (92.0; 100)	93.4 (86.2; 97.5)	76.9 (66.9; 85.1)	100 (95.7; 100)
% Seroresponse	-	-	95.0 (83.1; 99.4)	-	-	100 (92.0; 100)	-	-	97.6 (91.7; 99.7)
hSBA GMT	594 (445; 793)	103 (71.7; 149)	5894 (4325; 8031)	29.4 (20.1; 43.1)	11.6 (7.28; 18.3)	1592 (1165; 2174)	118 (79.3; 175)	31.8 (21.9; 46.1)	2969 (2293; 3844)
W									
% ≥1:8 (Seroprotection)	100 (91.6; 100)	97.6 (87.4; 99.9)	97.5 (86.8; 99.9)	95.9 (86.0; 99.5)	83.7 (70.3; 92.7)	100 (92.0; 100)	97.8 (92.3; 99.7)	90.1 (82.1; 95.4)	98.8 (93.5; 100)
% Seroresponse	-	-	97.5 (86.8; 99.9)	-	-	100 (92.0; 100)	-	-	98.8 (93.5; 100)
hSBA GMT	71.8 (53.3; 96.7)	50.0 (35.9; 69.5)	2656 (1601; 4406)	40.1 (30.6; 52.6)	21.2 (14.6; 30.9)	3444 (2387; 4970)	52.5 (42.7; 64.5)	31.5 (24.2; 41.0)	3043 (2248; 4120)
Y									
% ≥1:8 (Seroprotection)	100 (91.6; 100)	97.6 (87.4; 99.9)	100 (91.2; 100)	100 (92.7; 100)	89.8 (77.8; 96.6)	100 (92.0; 100)	100 (96.0; 100)	93.4 (86.2; 97.5)	100 (95.7; 100)
% Seroresponse	-	-	100 (91.2; 100)	-	-	100 (92.0; 100)	-	-	100 (95.7; 100)
hSBA GMT	105 (73.9; 149)	32.5 (24.8; 42.7)	2013 (1451; 2792)	75.8 (54.2; 106)	18.2 (13.8; 24.0)	2806 (2066; 3813)	88.1 (69.3; 112)	23.8 (19.4; 29.1)	2396 (1919; 2991)

* Clinical trial identifier MET54 – NCT03205358. The study was conducted in toddlers 12-23 months old.

** Clinical trial identifier MET62 – NCT03476135

$ N calculated using per protocol analysis set (PPAS) with valid serology results; booster dose = D30 MET62.

N calculated using full analysis set for persistence (FASP) with valid serology results; post-primary dose = D30 MET54, pre-booster dose = D0 MET62.

Vaccine seroresponse: titre is < 1:8 at baseline with post-vaccination titre ≥ 1:16 or titre is ≥ 1:8 at baseline with a ≥ 4-fold increase at post-vaccination.
95% CI of the single proportion calculated from the exact binomial method.

Children 2 through 9 years of age

Immunogenicity in subjects 2 through 9 years of age was evaluated in study MET35 (NCT03077438) (stratified by ages 2 through 5 and 6 through 9 years) comparing seroresponses following administration of either MenQuadfi or MenACWY-CRM.

Overall, for subjects 2 through 9 years of age, immune non-inferiority, based on hSBA seroresponse, was demonstrated for MenQuadfi as compared to MenACWY-CRM for all four serogroups.

Table 6: Comparison of bactericidal antibody responses to MenQuadfi and MenACWY-CRM 30 days after vaccination in meningococcal vaccine naïve subjects 2 through 5 years and 6 through 9 years of age (study MET35*)

	2-5 years		6-9 years	
Endpoint by Serogroup	**MenQuadfi (95% CI)**	**MenACWY-CRM (95% CI)**	**MenQuadfi (95% CI)**	**MenACWY-CRM (95% CI)**
A	N=227-228	N=221	N=228	N=237
% ≥1:8 (Seroprotection)	84.6 (79.3; 89.1)	76.5 (70.3; 81.9)	88.2 (83.2; 92.0)	81.9 (76.3; 86.5)
% Seroresponse	52.4 (45.7; 59.1)	44.8 (38.1; 51.6)	58.3 (51.6; 64.8)	50.6 (44.1; 57.2)
hSBA GMT	21.6 (18.2; 25.5)	18.9 (15.5; 23.0)	28.4 (23.9; 33.8)	26.8 (22.0; 32.6)
C	N=229	N=222-223	N=229	N=236
% ≥1:8 (Seroprotection)	97.4 (94.4; 99.0)	64.6 (57.9; 70.8)	98.3 (95.6; 99.5)	69.5 (63.2; 75.3)
% Seroresponse	94.3 (90.5; 96.9)	43.2 (36.6; 50.0)	96.1 (92.7; 98.2)	52.1 (45.5; 58.6)
hSBA GMT	208 (175; 246)	11.9 (9.79; 14.6)	272 (224; 330)	23.7 (18.2; 31.0)
W	N=229	N=222	N=229	N=237
% ≥1:8 (Seroprotection)	90.8 (86.3; 94.2)	80.6 (74.8; 85.6)	98.7 (96.2; 99.7)	91.6 (87.3; 94.8)
% Seroresponse	73.8 (67.6; 79.4)	61.3 (54.5; 67.7)	83.8 (78.4; 88.4)	66.7 (60.3; 72.6)
hSBA GMT	28.8 (24.6; 33.7)	20.1 (16.7; 24.2)	48.9 (42.5; 56.3)	33.6 (28.2; 40.1)

	2-5 years		6-9 years	
Endpoint by Serogroup	**MenQuadfi (95% CI)**	**MenACWY-CRM (95% CI)**	**MenQuadfi (95% CI)**	**MenACWY-CRM (95% CI)**
Y	N=229	N=222	N=229	N=237
% ≥1:8 (Seroprotection)	97.8 (95.0; 99.3)	86.9 (81.8; 91.1)	99.1 (96.9; 99.9)	94.5 (90.8; 97.0)
% Seroresponse	88.2 (83.3; 92.1)	77.0 (70.9; 82.4)	94.8 (91.0; 97.3)	81.4 (75.9; 86.2)
hSBA GMT	49.8 (43.0; 57.6)	36.1 (29.2; 44.7)	95.1 (80.2; 113)	51.8 (42.5; 63.2)

* Clinical trial identifier NCT03077438
N: number of subjects in the per-protocol analysis set with valid serology results.
95% CI of the single proportion calculated from the exact binomial method.

Children and adolescents 10 through 17 years of age

Immunogenicity in subjects aged 10 through 17 years of age was evaluated in two studies comparing seroresponses following administration of MenQuadfi compared to either MenACWY-CRM (MET50 [NCT02199691]) or MenACWY-DT (MET43 [NCT02842853]).

MET50 was conducted in meningococcal vaccine naïve subjects and seroresponse was evaluated following administration with either MenQuadfi alone, MenACWY-CRM alone, MenQuadfi co-administered with Tdap and HPV or Tdap and HPV alone.

Table 7: Comparison of bactericidal antibody responses to MenQuadfi and MenACWY-CRM 30 days after vaccination in meningococcal vaccine naïve subjects 10 through 17 years of age (study MET50*)

Endpoint by Serogroup	**MenQuadfi (95% CI)**		**MenACWY-CRM (95% CI)**	
A	N=463		N=464	
% ≥1:8 (Seroprotection)	93.5	(90.9; 95.6)	82.8	(79.0; 86.1)
% Seroresponse**#	75.6	(71.4; 79.4)	66.4	(61.9; 70.7)
hSBA GMT	44.1	(39.2; 49.6)	35.2	(30.3; 41.0)
C	N=462		N=463	
% ≥1:8 (Seroprotection)	98.5	(96.9; 99.4)	76.0	(71.9; 79.8)
% Seroresponse**#	97.2	(95.2; 98.5)	72.6	(68.3; 76.6)
hSBA GMT	387	(329; 456)	51.4	(41.2; 64.2)
W	N=463		N=464	
% ≥1:8 (Seroprotection)	99.1	(97.8; 99.8)	90.7	(87.7; 93.2)
% Seroresponse**#	86.2	(82.7; 89.2)	66.6	(62.1; 70.9)
hSBA GMT	86.9	(77.8; 97.0)	36.0	(31.5; 41.0)
Y	N=463		N=464	
% ≥1:8 (Seroprotection)	97.2	(95.2; 98.5)	83.2	(79.5; 86.5)
% Seroresponse**#	97.0	(95.0; 98.3)	80.8	(76.9; 84.3)
hSBA GMT	75.7	(66.2; 86.5)	27.6	(23.8; 32.1)

* Clinical trial identifier NCT02199691
N: number of subjects in the per-protocol analysis set with valid serology results.
95% CI of the single proportion calculated from the exact binomial method.

** Post-vaccination hSBA titres ≥1:8 for subjects with pre-vaccination hSBA titres < 1:8 or at least a 4-fold increase in hSBA titres from pre to post-vaccination for subjects with pre-vaccination hSBA titres ≥1:8
# Non-inferiority criterion met.

Study MET43 was performed to evaluate the immunogenicity of MenQuadfi compared to MenACWY-DT in children, adolescents and adults (10-55 years of age).

Table 8: Comparison of bactericidal antibody responses to MenQuadfi and MenACWY-DT 30 days after vaccination in meningococcal vaccine naïve subjects 10 through 17 years of age (study MET43*)

Endpoint by Serogroup	MenQuadfi (95% CI)		MenACWY-DT (95% CI)	
A	N=1,097		N=300	
% ≥1:8 (Seroprotection)	96.2	(94.9; 97.2)	89.0	(84.9; 92.3)
% Seroresponse**	74.0	(71.3; 76.6)	55.3	(49.5; 61.0)
hSBA GMT	78	(71.4; 85.2)	44.2	(36.4; 53.7)
C	N=1,097-1,098		N=300	
% ≥1:8 (Seroprotection)	98.5	(97.5; 99.1)	74.7	(69.3; 79.5)
% Seroresponse**	95.6	(94.2; 96.8)	53.3	(47.5; 59.1)
hSBA GMT	504	(456; 558)	44.1	(33.7; 57.8)
W	N=1,097		N=300	
% ≥1:8 (Seroprotection)	98.3	(97.3; 99.0)	93.7	(90.3; 96.1)
% Seroresponse**	84.5	(82.2; 86.6)	72.0	(66.6; 77.0)
hSBA GMT	97.2	(88.3; 107)	59.2	(49.1; 71.3)
Y	N=1,097		N=300	
% ≥1:8 (Seroprotection)	99.1	(98.3; 99.6)	94.3	(91.1; 96.7)
% Seroresponse**	95.6	(94.2; 96.8)	85.7	(81.2; 89.4)
hSBA GMT	208	(189; 228)	80.3	(65.6; 98.2)

* Clinical trial identifier NCT02842853
N: number of subjects in the per-protocol analysis set with valid serology results.
95% CI of the single proportion calculated from the exact binomial method.
** Non-inferiority criterion met.

Adults 18 through 55 years of age

Immunogenicity in subjects from 18 through 55 years of age was evaluated in study MET43 (NCT02842853) comparing MenQuadfi to MenACWY-DT.

Table 9: Comparison of bactericidal antibody responses to MenQuadfi and MenACWY-DT 30 days after vaccination in meningococcal vaccine naïve subjects 18 through 55 years of age (study MET43*)

Endpoint by Serogroup	**MenQuadfi (95% CI)**		**MenACWY-DT (95% CI)**	
A	N=1,406-1,408		N=293	
% ≥1:8 (Seroprotection)	93.5	(92.1; 94.8)	88.1	(83.8; 91.5)
% Seroresponse**	73.5	(71.2; 75.8)	53.9	(48.0; 59.7)
hSBA GMT	106	(97.2; 117)	52.3	(42.8; 63.9)
C	N=1,406-1,408		N=293	
% ≥1:8 (Seroprotection)	93.5	(92.0; 94.7)	77.8	(72.6; 82.4)
% Seroresponse**	83.4	(81.4; 85.3)	42.3	(36.6; 48.2)
hSBA GMT	234	(210; 261)	37.5	(29.0; 48.5)
W	N=1,408-1,410		N=293	
% ≥1:8 (Seroprotection)	94.5	(93.2; 95.7)	80.2	(75.2; 84.6)
% Seroresponse**	77.0	(74.7; 79.2)	50.2	(44.3; 56.0)
hSBA GMT	75.6	(68.7; 83.2)	33.2	(26.3; 42.0)
Y	N=1,408-1,410		N=293	
% ≥1:8 (Seroprotection)	98.6	(97.8; 99.1)	81.2	(76.3; 85.5)
% Seroresponse**	88.1	(86.3; 89.8)	60.8	(54.9; 66.4)
hSBA GMT	219	(200; 239)	54.6	(42.3; 70.5)

* Clinical trial identifier NCT02842853
N: number of subjects in the per-protocol analysis set with valid serology results.
95% CI of the single proportion calculated from the exact binomial method.
** Non-inferiority criterion met.

Adults 56 years of age and older

Immunogenicity in adults ≥ 56 years of age (mean 67.1 years, range 56.0 – 97.2 years) was assessed in study MET49 (NCT02842866) comparing the immunogenicity of MenQuadfi to MenACWY polysaccharide vaccine.

Table 10: Comparison of bactericidal antibody responses to MenQuadfi and MenACWY polysaccharide in meningococcal vaccine naïve in subjects 56 years of age and older 30 days after vaccination (study MET49*)

Serogroup Endpoint	**MenQuadfi (95% CI)**		**MenACWY polysaccharide (95% CI)**	
A	N=433		N=431	
% ≥1:8 (Seroprotection)	89.4	(86.1; 92.1)	84.2	(80.4; 87.5)
% Seroresponse**	58.2	(53.4; 62.9)	42.5	(37.7; 47.3)
hSBA GMT	55.1	(46.8; 65.0)	31.4	(26.9; 36.7)
C	N=433		N=431	
% ≥1:8 (Seroprotection)	90.1	(86.9; 92.7)	71.0	(66.5; 75.2)
% Seroresponse**	77.1	(72.9; 81.0)	49.7	(44.8; 54.5)
hSBA GMT	101	(83.8; 123)	24.7	(20.7; 29.5)

Serogroup Endpoint	MenQuadfi (95% CI)		MenACWY polysaccharide (95% CI)	
W	N=433		N=431	
% ≥1:8 (Seroprotection)	77.4	(73.1; 81.2)	63.1	(58.4; 67.7)
% Seroresponse**	62.6	(57.8; 67.2)	44.8	(40.0; 49.6)
hSBA GMT	28.1	(23.7; 33.3)	15.5	(13.0; 18.4)
Y	N=433		N=431	
% ≥1:8 (Seroprotection)	91.7	(88.7; 94.1)	67.7	(63.1; 72.1)
% Seroresponse**	74.4	(70.0; 78.4)	43.4	(38.7; 48.2)
hSBA GMT	69.1	(58.7; 81.4)	21.0	(17.4; 25.3)

* Clinical trial identifier NCT02842866
N: number of subjects in the per-protocol analysis set with valid serology results.
95% CI of the single proportion calculated from the exact binomial method.
** Non-inferiority criterion met.

Booster response

Study MET56 (NCT02752906) compared the immunogenicity of a booster dose of MenQuadfi with a booster dose of MenACWY-DT in subjects at least 15 years of age. These subjects were primed with a quadrivalent meningococcal conjugate vaccine (MenACWY-CRM (11.3%) or with MenACWY-DT (86.3%)) 4 to 10 years earlier.
At baseline, hSBA seroprotection and GMT were similar for serogroups A, C, W, and Y.

Table 11: Comparison of bactericidal antibody responses to MenQuadfi and MenACWY-DT 30 days after booster vaccination (study MET56*)

Serogroup Endpoint	MenQuadfi (95% CI)		MenACWY-DT (95% CI)	
A	N=384		N=389	
% ≥1:8 (Seroprotection)	100.0	(99.0; 100.0)	99.0	(97.4; 99.7)
% Seroresponse**	92.2	(89.0; 94.7)	87.1	(83.4; 90.3)
hSBA GMT	497	(436; 568)	296	(256; 343)
C	N=384		N=389	
% ≥1:8 (Seroprotection)	99.5	(98.1; 99.9)	99.0	(97.4; 99.7)
% Seroresponse**	97.1	(94.9; 98.6)	91.8	(88.6; 94.3)
hSBA GMT	2,618	(2,227; 3,078)	599	(504; 711)
W	N=384		N=389	
% ≥1:8 (Seroprotection)	100.0	(99.0; 100.0)	99.7	(98.6; 100.0)
% Seroresponse**	98.2	(96.3; 99.3)	90.7	(87.4; 93.4)
hSBA GMT	1,747	(1,508; 2,025)	723	(614; 853)
Y	N=384		N=389	
% ≥1:8 (Seroprotection)	99.7	(98.6; 100.0)	99.5	(98.2; 99.9)
% Seroresponse**	97.4	(95.3; 98.7)	95.6	(93.1; 97.4)
hSBA GMT	2,070	(1,807; 2,371)	811	(699; 941)

* Clinical trial identifier NCT02752906
N: number of subjects in the per-protocol analysis set with valid serology results.
95% CI of the single proportion calculated from the exact binomial method.
** Non-inferiority criterion met.

Clinical data on the persistence of antibody response 3 years after primary vaccination with MenQuadfi at 12-23 months of age are available in children 4-5 years of age. Clinical data on booster vaccination with MenQuadfi in those children are also available.

The European Medicines Agency has deferred the obligation to submit the results of studies within one or more subsets of the paediatric population under 12 months of age (see 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

No pharmacokinetic studies have been performed.

5.3 Preclinical safety data

Non-clinical safety data revealed no special risks for humans based on a developmental and reproductive toxicity study in female rabbits.

The administration of MenQuadfi to female rabbits at a full human dose showed no effects on mating performance, female fertility, no teratogenic potential, and no effect on pre- or post-natal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium acetate
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

42 months

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.

6.5 Nature and contents of container

Solution in a Type I borosilicate clear glass vial with a 13 mm chlorobutyl stopper and a flip off seal.
Pack of 1 or 5 single dose (0.5 mL) vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The vaccine should be inspected visually for any particulate matter and/or variation of physical aspect (or discolouration) prior to administration. In the event of either being observed, discard the vaccine.

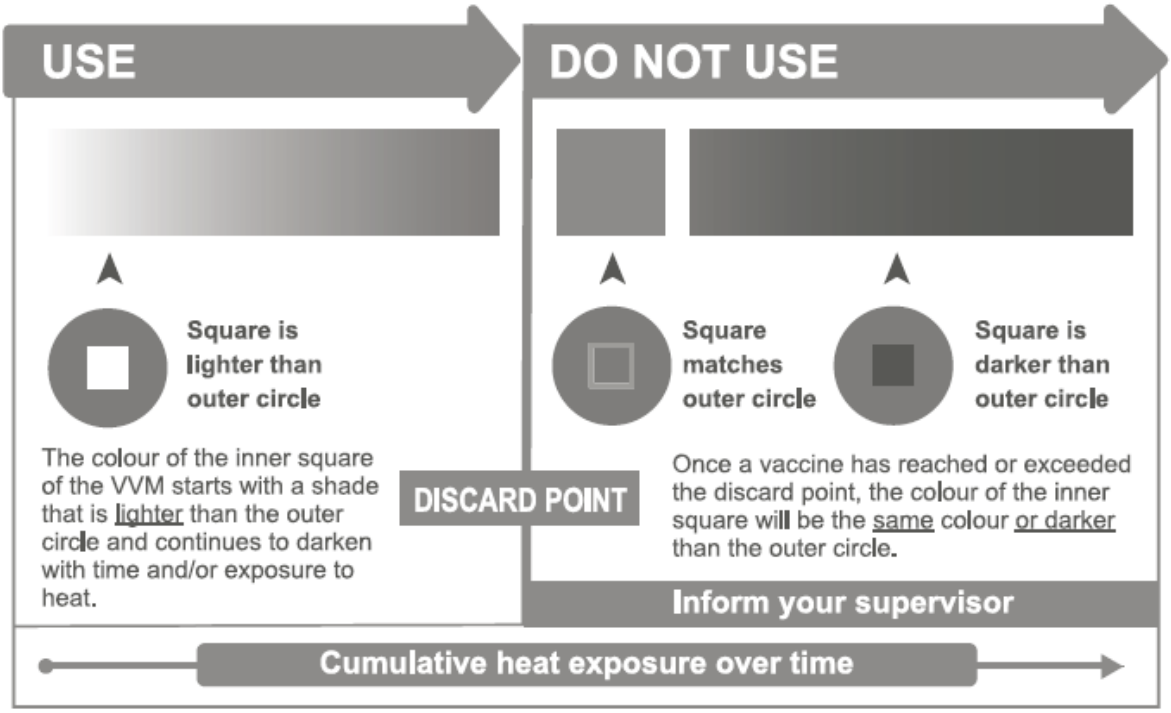
Preparation
Remove the flip off seal and using a suitable syringe and needle, withdraw 0.5 mL of solution, ensuring no air bubbles are present before injection.

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

Product Information as of February 2022.

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

The Vaccine Vial Monitors (VVM) are on the label of MenQuadfi vaccine supplied through SANOFI PASTEUR. The colour dot which appears on the label of the vial is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.



The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the circle, then the vaccine can be used. As soon as the colour of the central square is the same colour as the circle or of a darker colour than the circle, then the vial should be discarded.