Date: 6 March 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

MenQuadfi

International non-proprietary name: polysaccharida Neisseriae meningitidis (A, C, W-135, Y) conjugatum cum toxoidum tetani

Pharmaceutical form: solution for injection

Dosage strength(s): 0.5 ml

Route(s) of administration: intramuscular use

Marketing Authorisation Holder: Sanofi-Aventis (Suisse) SA

Marketing Authorisation No.: 68221

Decision and Decision date: approved on 5 October 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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Table of contents

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetic
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetic
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substances Neisseria meningitidis polysaccharides (A, C, W-135, Y) conjugated to tetanus toxoid of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

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.

2.2.2 Approved Indication

MenQuadfi is indicated for the 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. This vaccine should be used in accordance with official vaccination recommendations.

2.2.3 Requested Dosage

Primary vaccination:
- Individuals from 12 months: a single dose (0.5 ml)

Booster vaccination:
- A single dose of MenQuadfi (0.5 ml) may be administered to individuals who have received a monovalent meningococcal C conjugate vaccine or another quadrivalent meningococcal vaccine with the same serotypes.
- There are no data to determine the need and the timepoint of a booster vaccine in individuals who have received the primary vaccination with MenQuadfi.

Other paediatric patients:
- The safety and immunogenicity of MenQuadfi in individuals younger than 12 months.

Only for intramuscular administration.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	1 October 2020
Formal control completed	26 October 2020
List of Questions (LoQ)	23 February 2021
Answers to LoQ	17 May 2021
Predecision	19 August 2021
Answers to Predecision	3 November 2021
2nd Predecision	1 February 2022
Answers to 2nd Predecision	25 March 2022
Labelling corrections	22 June 2022
Answers to Labelling corrections	13 July 2022
Final Decision	5 October 2022
Decision	approval

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3 Medical Context

Neisseria meningitidis, also known as meningococcus, is a gram-negative diplococcus that causes a disease with a clinical presentation of meningitis, bacteraemia (meningococcaemia) or both. Meningococcal disease can also present as focal infections such as pneumonia, arthritis or pericarditis. Meningococcal disease develops rapidly, often among previously healthy persons, and results in high morbidity and mortality.

Invasive meningococcal disease (IMD) is a major cause of meningitis and septicaemia. The disease often has a rapid progression, with an 8–15% case fatality rate even with appropriate antibiotic therapy. 10%–20% of survivors have long-term sequelae such as neurological disability, limb or digit loss, or hearing loss.[1]
The highest incidence occurs in young children, with a second disease peak among adolescents and young adults.

Meningococci are divided into antigenically distinct serogroups. Twelve capsular groups have been identified to date: A, B, C, E, H, I, K, L, W, X, Y and Z. Groups B, C, W and Y were historically the most common in Europe. Following the routine vaccination against serogroup C, serogroup B has become the most common, with an increase in W and Y serogroups in recent years, especially among adolescents.

Outbreaks of meningococcal disease are rare, but can occur in settings where people assemble, such as college campuses and military recruits.

For the immunisation against meningococcal disease, several vaccines are available for different age groups with different vaccination schedules. Some are monovalent, with a single serogroup (monovalent C vaccines and a meningococcal B vaccine), and another is a quadrivalent vaccine including the A, C, W and Y serogroups.

Regarding the national meningococcal vaccine recommendations, please refer to the Swiss vaccination schedule issued by the Federal Vaccination Commission and the Federal Office of Public Health.

[1] Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020 | MMWR (cdc.gov)

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4 Quality Aspects

4.1 Drug Substance

The active substance consists of four bulks of polysaccharide tetanus toxoid conjugate concentrate from the Neisseria meningitidis serogroups A, C, W135 and Y. The conjugated antigens used in this vaccine are intended to elicit a serological immune response upon injection by the production of bactericidal antibodies specific to the respective capsular polysaccharides. The drug substance is manufactured by propagation and fermentation of the working seeds of each N. meningitidis serogroup strain. The fermentation broth is processed by multiple steps, including inactivation, ethanol precipitation, filtration, washing and drying. The purified polysaccharide powder is individually coupled to tetanus toxoid, which is prepared by fermentation of a Clostridium tetani working seed, cell lysis, purification of the toxin, inactivation of the toxin to the toxoid and purification of the toxoid. The manufacturing process is adequately controlled and has been validated with full-scale batches. The characterisation of the drug substance and its impurities was performed using state of the art methods (e.g. 1D-Proton-NMR, HPSEC-MALS, DSC, SDS PAGE, MALDI-TOF, LC-MS). The specifications include identity tests, purity and residual tests, sterility and endotoxins. Batch analysis data from commercial scale batches show that the drug substance can be manufactured consistently and to defined quality standards. All analytical methods are described and validated. The drug substance is stored at -80°C to -60°C. A shelf life of 48 months has been accepted.

4.2 Drug Product

The finished product is supplied in liquid form filled in 2 mL unit dose vials. Each labelled vial contains a 0.5 mL dose. The formulation is prepared to contain 10 µg of each of the meningococcal polysaccharide serogroups A, C, W and Y, conjugated to approximately 55 µg tetanus toxoid protein carrier in a sodium acetate buffered saline solution. The finished product manufacturing process includes blending of the four monovalent conjugate bulks, sterile filtration and filling. Process validation studies were conducted at commercial scale. The specifications include relevant tests and limits, e.g. for appearance, potency, pH, identity, purity, sterility and endotoxins.
All analytical methods are adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. Batch analysis data were provided for three consistency/process validation batches, four batches at the lower commercial scale and three batches at the higher commercial scale. The container closure system for the final product consists of a type I glass vial with a latex-free stopper and a flip-off seal. The drug product is stored at 2 – 8°C. No significant changes are observed over time during stability studies within the proposed storage conditions. A shelf life of 48 months has been accepted. The product should not be frozen and should be kept in the outer carton.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Regarding the marketing authorisation application of MenQuadfi, the Division Preclinical Review conducted an abridged evaluation, which was based on the EMA assessment report (17.09.2020) provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of MenQuadfi 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 pharmaco-toxicological profile has been sufficiently characterised. There were no safety issues identified in the nonclinical studies that would be of concern for human use. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

No pharmacokinetic studies were conducted, which is acceptable and in accordance with the EMA Guideline on “the Clinical Evaluation of New Vaccines” (EMEA/CHMP/VWP/164653/2005).
Anti-capsular meningococcal antibodies protect against meningococcal diseases via complement-mediated bactericidal activity.
Quadrivalent meningococcal conjugate vaccines induce the production of bactericidal antibodies specific to the capsular polysaccharides of Neisseria meningitidis serogroups A, C, W and Y.
Human bactericidal activity with human complement (hSBA) can be used to infer effectiveness of meningococcal conjugate vaccines.
The serum bactericidal activity (SBA) assay has been the accepted surrogate marker for meningococcal vaccine efficacy since the mid-1970s, established by the findings of Goldschneider et al.[2]
A hSBA titre of ≥1:8 and/or a fourfold rise in hSBA titres have been used to infer vaccine-mediated immunologic protection against meningococcal disease.
Most of the submitted studies assessed the immunogenicity based on hSBA titres, for vaccine seroresponse (defined as titres ≥1:16 if pre-vaccination titres were <1:8, or titres ≥ 4-fold if pre-vaccination titres were ≥1:8), for seroprotection rates (defined as hSBA titres ≥1:8) and for GMTs, although some studies concomitantly used rSBA (serum bactericidal assay using rabbit complement) titres as well.

6.2 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

For the marketing authorisation application of MenQuadfi, Clinical Assessment conducted an abridged evaluation for the population aged 2 years and above, based on the EMA assessment report (EMA/CHMP/452679/2020) and the corresponding SmPC provided by the applicant.

Our clinical review primarily focused on the data from the 12-23 month-old population, as the initially submitted clinical data package was considered limited for this age group. The immunogenicity and safety of MenQuadfi in toddlers aged 12-23 months were assessed in the pivotal Study MET 51 and supportive study MET54. Study MET 57 evaluated the safety and immunogenicity of MenQuadfi co-administration with other paediatric vaccines.

Based on the submitted studies, the antibody persistence beyond 30 days post-vaccination was not evaluated, and the safety profile in the above age group was assessed mostly up to 30 days post-vaccination. Additionally, the comparator vaccine used in the toddler studies was a conjugated quadrivalent meningococcal vaccine not authorised in Switzerland.

The antibody levels against the serogroups should be assessed beyond 30 days post-vaccination, especially in toddlers as, like infants, they are especially prone to develop invasive meningococcal disease. The rapid waning of the antibodies against serogroup A is known for other quadrivalent meningococcal vaccines. In particular, the seroresponse rates for serogroup A were consistently the lowest among the four serogroups for MenQuadfi. Furthermore, in Study MET51 in toddlers, the immune response against serogroup W was also weaker compared to the other two serogroups, and the assessment of the antibody levels beyond 30 days was of the utmost importance and was additionally required.

Study MET51 was a modified double-blind, randomised, parallel-group, active-controlled, multi-centre trial in toddlers, 12 to 23 months of age, who were either meningococcal vaccine-naïve or had received monovalent meningococcal C (MenC) vaccination during infancy.

[2] Goldschneider et al 1969

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Based on the results of Study MET51, the immunogenicity of MenQuadfi was shown to be non-inferior to the comparator vaccine 30 days post-vaccination (Table 1 in the Information for healthcare professionals), however an impact of the MenC priming could not be ruled out as differences could be observed depending on previously received MenC conjugate protein. However the clinical relevance of the lower hSBA titres with similar seroprotection rates seen in children primed with a Men C-CRM vaccine in infancy is not known, considerations should be given in individuals at high risk of meningococcal A infection.
The data separately for the MenC-TT and MenC-CRM priming are presented in a tabulated form in Table 2 in the Information for healthcare professionals.

Study MET 54 was a phase 2, randomised, parallel active-controlled, open-label study in 200 healthy, meningococcal-vaccine naïve toddlers aged 12 to 23 months in Finland. It evaluated the immunogenicity and safety profile of a single dose of MenQuadfi given alone compared to that of a quadrivalent meningococcal conjugate vaccine licensed in Europe but not in Switzerland.
The immunogenicity results showed that the hSBA GMTs at day 30 post-vaccination for serogroups A and Y were comparable with, and for serogroups C and W were higher than, the comparator vaccine. The rate of seroprotection (subjects with hSBA titres ≥ 1:8) were comparable between the vaccine groups.

Study MET57 was a phase 3, open-label (immunology laboratory technicians were blinded to group assignment), randomised, parallel-group, active-controlled, multi-centre study in 1200 healthy toddlers aged 12 to 23 months. It described the immunogenicity and safety of a single dose of MenQuadfi administered alone and concomitantly with other paediatric vaccine(s) in South Korea and Thailand (measles-mumps-rubella [MMR] vaccine + varicella [V] vaccine), Mexico (diphtheria, tetanus, acellular pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type-b [DTaP-IPV-HB-Hib] conjugate vaccine) and the Russian Federation (pneumococcal conjugate vaccine [PCV13]).
The results showed that the immune response was the weakest for the serogroup A when the MenQuadfi was administered alone. The immunogenicity data were suggestive of a lower seroresponse rate, with significantly lower GMTs for serogroup A when co-administered with PCV13. The clinical relevance of this observation is not known, but this observation could be considered in individuals at high risk of meningococcal A infection, and consequently vaccination with MenQuadfi and PCV-13 could be performed separately. The results are presented in the Information for healthcare professionals.

During the assessment process, newly available results from a long-term immune persistence study were provided. Study MET62 provided information on the immune persistence at three years following a primary vaccination (in study MET54) at 12 to 23 months of age with MenQuadfi or a comparator quadrivalent conjugated meningococcal vaccine in a total of 91 participants. The results showed an expected decrease in the GMTs between Day 30 post-primary vaccination (MET54) and Day 0 (MET62) for all serogroups for both vaccines. Somewhat lower hSBA GMTs and seroprotection rates ≥ 1:8 were observed for serogroup A in the MenQuadfi primed group after 3 years compared to the control group. There were otherwise comparable or better results with MenQuadfi. For the other serogroups (C, W, Y) a high-level immune persistence (GMT and seroprotection rates ≥ 1:8) was observed. For all the serogroups a high booster response at Day 30 (MET62) were seen. For a detailed, tabulated presentation of the immune persistence and the booster responses, please refer to Table 3 in the Information for healthcare professionals.

The safety profile of MenQuadfi was considered acceptable, for details please refer to the EMA assessment report (EMA/CHMP/452679/2020).The nature and frequency of the reported adverse events were considered to be consistent with those expected after vaccine administration, were comparable with those observed for the comparator vaccines and did not give cause for concern. However, for toddlers 12-23 months of age the safety profile of MenQuadfi could not be fully characterised beyond 30 days, as data were very limited.

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As the amounts of the antigens for each serogroup are higher in MenQuadfi than in the other quadrivalent conjugated polysaccharide meningococcal vaccines, the experience from these vaccines cannot be fully relied on. The safety findings in different older age groups were considered supportive, although did not substitute the clinical safety results specific for this age group.

It is preferable for unsolicited adverse events and SAEs to be collected for at least 6 months after vaccination. In order to further characterise the safety profile of MenQuadfi in 12-23 month-old toddlers, the applicant is required to provide further safety data from ongoing toddler studies with a 6-month safety follow-up period (post-approval requirement).

Overall, the submitted clinical documentation on the immunogenicity and safety of MenQuadfi with the additionally provided study results and the post-approval requirements were considered appropriate to support the approval 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.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to MenQuadfi, solution for injection was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

MenQuadfi, Meningococcal Group A, C, W and Y-Polysaccharide conjugate vaccine

Composition

Active substances

Neisseria meningitidis group A, C, W-135 and Y polysaccharides conjugated to tetanus toxoid carrier protein.

Excipients

Sodium chloride
Sodium acetate
Water for injections
This medicine contains 1.67 mg sodium per dose.

Pharmaceutical form and active substance quantity per unit

Ready to use solution for injection.
Clear colourless solution.

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-135 polysaccharide[1]	10 micrograms

[1]Conjugated to tetanus toxoid carrier protein 55 micrograms.

Indications/Uses

MenQuadfi is indicated for the active immunisation of individuals from the age of 12 months and older against invasive meningococcal disease caused by *Neisseria meningitidis* of serogroups A, C, W, and Y.
This vaccine should be used in accordance with official vaccination recommendations.

Dosage/Administration

Primary Vaccination:

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

Booster Vaccination:

- A single dose (0.5 mL) of MenQuadfi may be used to boost subjects who have previously received a meningococcal conjugate vaccine containing the same serogroups (see section “Clinical efficacy”)
- There are no data available to indicate the need for or timing of a booster dose of MenQuadfi for individuals who have been primed with MenQuadfi.

Other Paediatric Population

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

Mode of administration

For intramuscular injection only. Depending on the recipient’s age and muscle mass, the injection should be carried out preferably into the upper arm (deltoid muscle) or the anterolateral thigh region. To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Contraindications

Hypersensitivity to the active substances or to any of the excipients (including tetanus toxoid) or after previous administration of the vaccine or a vaccine containing the same components.

Warnings and precautions

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.
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.
Vaccination should be postponed in individuals suffering from an acute severe febrile illness. However, the presence of a minor infection should not result in the deferral of vaccination.
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 and injury and to manage syncope.
Following vaccination with another conjugated quadrivalent meningococcal vaccine (ACWY-D)*, there was evidence of a potential increase in the risk of developing Guillain-Barré syndrome based on pharmacovigilance data. There are no data currently available to assess the potential risk following the use of MenQuadfi.
*Not approved in Switzerland.

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.
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.
A decrease in serum bactericidal antibody titers 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. There are no data available for MenQuadfi.
Lower hSBA geometric mean titers (GMTs) against serogroup A have been observed after a single dose of MenQuadfi was administered to infants previously primed with serogroup C meningococcal conjugate vaccine (MenC-CRM) during infancy. Nevertheless, seroprotection rates were comparable among treatment groups of MenC-primed infants (see section “Clinical efficacy”). 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.
It is possible that in individuals receiving immunosuppressive treatment or suffering from immunodeficiency, an adequate immune response may not be elicited. Individuals with familial complement deficiencies (for example, C5 or C3 deficiencies) as well as individuals receiving treatments that inhibit terminal complement activation 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. There are no data available on the use in immunocompromised patients.
Vaccination with MenQuadfi does not substitute for routine tetanus vaccination.
Co-administration of MenQuadfi with a tetanus toxoid-containing vaccine does not impair the response to tetanus toxoid or impact the safety.
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

Interactions

Injection sites on separate limbs and separate syringes must be used in the case of concomitant administration with other medicinal products.
For ages 12–23 months, MenQuadfi was evaluated in a clinical trial along with the Measles-mumps-rubella (MMR) vaccine and Varicella (V) vaccine, combined Diphtheria, Tetanus and 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 vaccine and 13-valent Pneumococcal polysaccharides conjugate vaccines (PCV13) (see section “Undesirable effects”).
Lower hSBA GMTs on day 30 post-dose for serogroup A have been observed when MenQuadfi was administered concomitantly with PCV-13. The clinical relevance of this observation is unknown. As a

precaution, separate administration of MenQuadfi and PCV-13 vaccines should be considered in children 12–23 months of age at high risk for serogroup A disease.
For ages 10–17 years, MenQuadfi was evaluated in a clinical trial along with Diphtheria, Tetanus and Pertussis (acellular, component) Vaccine (adsorbed, reduced antigen(s) content) (Tdap) and Human Papillomavirus Vaccines (recombinant, adsorbed) (HPV).
In children and adolescents (10–17 years of age), who had not received meningococcal vaccination, the immune response to MenQuadfi as well as to the diphtheria, tetanus or HPV vaccine components was not adversely impacted by the concomitant administration.
Meningococcal vaccine naïve children and adolescents aged 10–17 years had no inferior response to PT and lower antibody responses to FHA, PRN and FIM when MenQuadfi was administered concomitantly with Tdap and HPV vaccine compared to co-administration with HPV vaccine alone. Similar results have been reported with other quadrivalent meningococcal conjugate vaccines. Since there is no established correlate of protection for pertussis, the clinical relevance of this observation is unknown.
Concomitant administration of MenQuadfi with other vaccines than those previously mentioned has not been studied.

Pregnancy, lactation

Pregnancy

There are no clinical 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 “Preclinical data”). MenQuadfi should be used during pregnancy only if the potential benefits to the mother outweigh the potential risks, including those to the foetus.

Lactation

It is unknown whether MenQuadfi is excreted in human milk. MenQuadfi should be used during breast-feeding only if the potential benefits to the mother outweigh the potential risks, including those to the breastfed child.

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 “Preclinical data”).

Effects on ability to drive and use machines

MenQuadfi has no influence on the ability to drive and use machines.
However, some of the effects mentioned under section “Undesirable effects” may temporarily affect the ability to drive or use machines.

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-center pivotal studies. In these studies, a total of 6,308 participants received either a primary dose (N = 5,906) or a booster dose (N = 402) of MenQuadfi and were included in the safety analyses. Participants aged 2 years and older were monitored for 6 months post-vaccination and participants 12 to 23 months of age were monitored for 30 days post-vaccination. This total included 1,389 infants aged 12 to 23 months of age, 498 children aged 2 to 9 years, 2,289 adolescents aged 10 to 17 years, 1,684 adults aged 18 to 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 infants received MenQuadfi co-administered with MMR+V (N = 189), DTaP-IPV-HB-Hib (N = 200) or PCV13 (N = 200).

The most common occurring adverse reactions within 7 days of vaccination with a single dose of MenQuadfi alone in infants 12 to 23 months of age were irritability (36.7 %) and injection site tenderness (30.6 %) and in ages 2 years and older were injection site pain (38.7 %) and myalgia (30.5 %). These adverse reactions were mostly mild or moderate in intensity.
The incidence of adverse reactions after a booster dose of MenQuadfi in adolescents and adults 15 years of age and older was comparable to that seen among adolescents and adults who received a primary dose of MenQuadfi.

Rates of adverse reactions within 7 days of vaccination among infants were comparable when MMR+V was administered concomitantly with or without MenQuadfi, and when DTaP-IPV-HB-Hib was administered with or without MenQuadfi. Overall, the rates of adverse reactions were higher in infants who received PCV-13 given concomitantly with MenQuadfi (36.5 %) than in infants who received PCV-13 alone (17.2 %).
The following adverse reactions, as listed below, have been identified from five clinical studies conducted with MenQuadfi when given alone to individuals 2 years of age and older. The safety profile observed in infants ages 12 to 23 months is presented in the section “Paediatric population”.
The adverse reactions should be arranged according to MedDRA system organ classes and the conventional frequencies as follows:
"very common" (≥ 1/10)
"common" (≥ 1/100, < 1/10),
"uncommon" (≥ 1/1,000, < 1/100)
"rare" (≥ 1/10,000, < 1/ 1,000).

Adverse reactions following administration of MenQuadfi from clinical trials in individuals 2 years of age and above:

Blood and lymphatic system disorders

Rare: Lymphadenopathy.

Nervous system disorders

Very common: Headache (26.5 %).

Uncommon: Dizziness.

Gastrointestinal disorders

Uncommon: Nausea, vomiting.

Rare: Diarrhoea, stomach pain.

Skin and subcutaneous tissue disorders

Rare: Urticaria, pruritus, rash.

Musculoskeletal and connective tissue disorders

Very common: Myalgia (30.5 %).

Rare: Pain in extremity.

General disorders and administration site conditions

Very common: Injection site pain (38.7 %), malaise (21.7 %).

Common: Fever, injection site reactions (swelling, erythema).

Uncommon: Tiredness, injection site reactions (pruritus, warmth, bruising, rash).

Rare: Chills, armpit pain, injection site induration.

Paediatric population

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

Injection site reactions within 7 days were more commonly observed after booster vaccination in children 4 to 5 years of age (MET62) who were previously vaccinated 3 years earlier in MET54. The most common injection site reactions after MenQuadfi booster dose were pain (61.9 % in subjects primed with MenQuadfi vs. 71.4 % in subjects primed with MenACWY-TT), erythema (52.4 % vs. 55.1 %) and swelling (38.1 % vs. 38.8 %). These adverse reactions were mild or moderate in intensity.

In infants 12 to 23 months of age, injection site erythema and swelling (very common) at the injection site of MenQuadfi, as well as vomiting (common) and diarrhoea (common) were reported more frequently than in older age groups.

Adverse reactions following administration of MenQuadfi from clinical trials in individuals 12 months to 23 months:

Nervous system disorders

Very common: Drowsiness (18.9 %).

Gastrointestinal disorders

Common: Vomiting, diarrhoea.

Skin and subcutaneous tissue disorders

Uncommon: Urticaria.

Psychiatric disorders

Very common: Irritability (36.7 %).

Metabolism and nutrition disorders

Very common: Appetite lost (25.7 %).

General disorders and administration site conditions

Very common: Abnormal crying (26.2 %), injection site reactions (tenderness/pain [30.6 %], erythema [29.9 %], swelling [16.8 %]).

Common: Fever.

Uncommon: At the injection site: pruritus, induration, bruising, rash.

Older population (> 55 years of age)

Overall, the same injection site and systemic adverse reactions but at lower frequencies were observed within seven days of vaccination with a single dose of MenQuadfi in older adults (56 years of age and older) than in younger adults (18 to 55 years old). Only injection site pruritus has been reported more frequently in older adults. These adverse reactions mostly were mild or moderate in intensity.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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.

Properties/Effects

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.

Pharmacodynamics

Pharmacotherapeutic group: meningococcal vaccines

Clinical efficacy

Immunogenicity
The immunogenicity of a single dose of MenQuadfi for primary vaccination in infants (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 older) was assessed in 6 studies. The immunogenicity of a single dose of MenQuadfi for booster vaccination (ages 15 to 55 years, participants previously vaccinated with another meningococcal vaccine) was assessed in one pivotal study.
Clinical data on the persistence of antibody response 3 years after primary vaccination with MenQuadfi at 12–23 months of age are available for children 4–5 years of age. Clinical data on booster vaccination with MenQuadfi in these children are also available.

Infants 12 to 23 months of age
Immunogenicity in participants 12 to 23 months of age was evaluated in two clinical studies (MET51 and MET57).

Table 1: Comparison of Bactericidal Antibody Responses to MenQuadfi and MenACWY-TT vaccine 30 Days after Vaccination of Meningococcal Vaccine Naïve Participants only or Combined (Naïve + MenC Primed) Participants 12 to 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)

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)
% 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; 1,035)	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)

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

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

* The response of subjects with an hSBA titer < 1 : 8 at baseline who then achieved an hSBA titer ≥ 1 : 16 or the response of subjects with an hSBA titer ≥ 1 : 8 at baseline who then achieved a ≥ 4-fold increase in hSBA titer.

** Non-inferiority criterion met.

- *Response in participants previously vaccinated with MenC conjugate vaccines in their first year of life*

The majority of monovalent meningococcal C conjugate vaccine primed infants (12–23 months of age) in study MET51 had hSBA titers ≥ 1 : 8: in the MenQuadfi group (N = 198) ≥ 86.7 % and in

MenACWY-TT group (N = 99) ≥ 85.7 %, each at day 30 after receiving MenQuadfi or MenACWY-TT. These infants had received during their infancy either MenC-TT or MenC-CRM vaccines. The post vaccination seroprotection rates were comparable between MenQuadfi and MenACWY-TT for all serogroups regardless of the priming background.

Among subjects primed with MenC-CRM, 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 MenQuadfi administration, seroprotection rates (hSBA titers ≥ 1 : 8) were lower in subjects primed with MenC-CRM 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]). Serogroup Y rates 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]). Serogroup C seroprotection rates 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 could be considered in individuals at high risk for MenA infection who received the MenC-CRM vaccine in their first year of life.

Table 2: -MET51 – Comparison of Bactericidal Antibody Responses to MenQuadfi and MenACWY-TT vaccine 30 days after Vaccination of Meningococcal primed Participants 12 to 23 months of Age – By type on MenC priming (Study MET51)

Endpoint by serogroup	MenQuadfi		MenACWY-TT	
	MenC-TT primed (95 % CI)	MenC-CRM primed (95 % CI)	MenC-TT primed (95 % CI)	MenC-CRM primed (95 % CI)
A	N = 149	N = 48	N = 73–74	N = 25
% ≥ 1 : 8 (Seroprotection)	96.6 (92.3; 98.9)	68.8 (53.7; 81.3)	98.6 (92.7; 100.0)	96.0 (79.6; 99.9)
% seroresponse*	84.6 (77.7; 90.0)	50.0 (35.2; 64.8)	93.2 (84.7; 97.7)	84.0 (63.9; 95.5)
hSBA GMT	43.5 (36.2; 52.2)	12.0 (8.23; 17.5)	73.7 (56.9; 95.3)	42.2 (25.9; 68.8)
C	N = 149	N = 47	N = 73–74	N = 25
% ≥ 1 : 8 (Seroprotection)	100.0 (97.6; 100.0)	95.7 (85.5; 99.5)	100.0 (95.1; 100.0)	92.0 (74.0; 99.0)
% seroresponse*	96.6 (92.3; 98.9)	91.5 (79.6; 97.6)	95.9 (88.5; 99.1)	92.0 (74.0; 99.0)
hSBA GMT	6,026 (4,915; 7,389)	157 (94.9; 261)	3,945 (2,891; 5,385)	211 (98.7; 451)
W	N = 149	N = 47	N = 73–74	N = 24
% ≥ 1 : 8 (Seroprotection)	92.6 (87.2; 96.3)	68.1 (52.9; 80.9)	87.8 (78.2; 94.3)	79.2 (57.8; 92.9)
% seroresponse*	85.2 (78.5; 90.5)	44.7 (30.2; 59.9)	78.1 (66.9; 86.9)	62.5 (40.6; 81.2)
hSBA GMT	37.1 (30.7; 44.9)	12.6 (8.30; 19.2)	24.6 (19.0; 31.9)	16.5 (9.64; 28.1)
Y	N = 148–149	N = 47-48	N = 73–74	N = 25
% ≥ 1 : 8 (Seroprotection)	96.0 (91.4; 98.5)	95.8 (85.7; 99.5)	95.9 (88.6; 99.2)	80.0 (59.3; 93.2)
% seroresponse*	91.9 (86.3; 95.7)	80.9 (66.7; 90.9)	82.2 (71.5; 90.2)	68.0 (46.5; 85.1)
hSBA GMT	53.9 (44.8; 64.8)	33.4 (23.2; 48.2)	32.9 (26.0; 41.6)	27.1 (14.3; 51.5)

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

* Vaccine seroresponse: titer is < 1 : 8 at baseline with post-vaccination titer ≥ 1 : 16 or titer is ≥ 1 : 8 at baseline with a ≥ 4-fold increase at post vaccination.

MET57 was conducted in meningococcal vaccine naïve infants 12 to 23 months of age to assess the immunogenicity of concomitant administration of MenQuadfi with paediatric vaccines (MMR+V, DTaP-IPV-HB-Hib or PCV-13). The study showed post-vaccination hSBA seroprotection rates in participants vaccinated with MenQuadfi ranged from 88.9 % to 100 % for all serogroups between.
Serum antibody response and seroprotection rates for serogroup A were comparable when MenQuadfi was co-administered with PCV-13 and administered 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 hSBA-GMTs for serogroup A when MenQuadfi was co-administered with PCV-13 (N = 196) compared with MenQuadfi alone (N = 96) (24.6 [95 % CI 20.2; 30.1] and 49.0 [95 % CI 36.8; 65.3]). The clinical relevance of this observation is unknown, but this observation could be considered in persons at high risk for MenA infection, and consequently, vaccination with MenQuadfi and PCV-13 could be administered separately.

Immunogenicity booster and persistence response:
MET62 evaluated the antibody persistence of a primary dose and the antibody response to a booster dose of MenQuadfi in children 4–5 years of age who had received a single dose of MenQuadfi or MenACWY-TT three years prior at 12–23 months of age in study MET54 (phase II, study comparing the safety and immunogenicity of MenQuadfi with MenACWY-TT in infants [12–23 months]) (see table 3).

Table 3: 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* (12–23 months of age) – (study MET62)**

Serogroup 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)
% Serorespo nse	-	-	100 (91.2; 100)	-	-	95.5 (84.5; 99.4)	-	-	97.6 (91.7; 99.7)
hSBA GMT	83.3	11.9	763 (521; 1117)	49.6	14.7	659 (427; 1017)	63.0	13.3	706 (531; 940)

Serogroup 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)		
	(63.9; 109)	(8.11; 17.4)		(32.1; 76.7)	(10.7; 20.2)		(48.3; 82.2)	(10.5; 17.0)	
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)	5,894 (4,325; 8,031)	29.4 (20.1; 43.1)	11.6 (7.28; 18.3)	1,592 (1,165; 2,174)	118 (79.3; 175)	31.8 (21.9; 46.1)	2,969 (2,293; 3,844)
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)	2,656 (1,601; 4,406)	40.1 (30.6; 52.6)	21.2 (14.6; 30.9)	3,444 (2,387; 4,970)	52.5 (42.7; 64.5)	31.5 (24.2; 41.0)	3,043 (2,248; 4,120)
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 (1,451; 2,792)	75.8 (54.2; 106)	18.2 (13.8; 24.0)	2,806 (2,066; 3,813)	88.1 (69.3; 112)	23.8 (19.4; 29.1)	2,396 (1,919; 2,991)

*MET54 – NCT03205358. The study was conducted in infants 12–23 months old.

**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: titer is < 1 : 8 at baseline with post-vaccination titer ≥ 1 : 16 or titer 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 to 9 years of age

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

Overall, for participants 2 to 9 years of age, immune non-inferiority, based on hSBA seroresponse, was demonstrated for MenQuadfi as compared to MenACWY-CRM for all four serogroups (see table 4).

Table 4: Comparison of Bactericidal Antibody Responses to MenQuadfi and MenACWY-CRM 30 Days after Vaccination in Meningococcal Vaccine Naïve Participants 2 to 5 Years and 6 to 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)
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)

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.
* The response of subjects with an hSBA titer < 1 : 8 at baseline who then achieved an hSBA titer ≥ 1 : 16 or the response of subjects with an hSBA titer ≥ 1 : 8 at baseline who then achieved a ≥ 4-fold increase in hSBA titer.

Children and Adolescents 10 to 17 Years of Age

Immunogenicity in participants aged 10 to 17 years of age was evaluated in two studies comparing seroresponses following administration of MenQuadfi and MenACWY-CRM (MET50) or MenACWY-DT (MET43).

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

Table 5: Comparison of Bactericidal Antibody Responses to MenQuadfi and MENACWY-CRM 30 Days after Vaccination in Meningococcal Vaccine Naïve Participants 10 to 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)

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.

**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

Non-inferiority criterion met.

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

Table 6: Comparison of Bactericidal Antibody Responses to MenQuadfi and MenACWY-DT 30 Days after Vaccination in Meningococcal Vaccine Naïve Participants 10 to 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)

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.

**The response of subjects with an hSBA titer < 1 : 8 at baseline who then achieved an hSBA titer ≥ 1 : 16 or the response of subjects with an hSBA titer ≥ 1 : 8 at baseline who then achieved a ≥ 4-fold increase in hSBA titer. Non-inferiority criterion met.

Adults 18 to 55 Years of Age

Immunogenicity in participants 18 to 55 years of age was evaluated in study MET43 comparing MenQuadfi to MenACWY-DT.

Table 7: Comparison of Bactericidal Antibody Responses to MenQuadfi and MenACWY-DT 30 Days after Vaccination in Meningococcal Vaccine Naïve Participants 18 to 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)

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.

** The response of subjects with an hSBA titer < 1 : 8 at baseline who then achieved an hSBA titer ≥ 1 : 16 or the response of subjects with an hSBA titer ≥ 1 : 8 at baseline who then achieved a ≥ 4-fold increase in hSBA titer. Non-inferiority criterion met.

Adults 56 Years of Age and Older

Immunogenicity in adults ≥ 56 years of age was assessed in study MET49 comparing MenQuadfi to MenACWY polysaccharide vaccine.

In study MET49, the overall mean age of participants vaccinated with MenQuadfi was 66.9 years. The age range of participants was 56 to 96 years of age.

Table 8: Comparison of Bactericidal Antibody Responses to MenQuadfi and MenACWY polysaccharide in Meningococcal Vaccine Naïve Participants 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)
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)

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.

** The response of subjects with an hSBA titer < 1 : 8 at baseline who then achieved an hSBA titer ≥ 1 : 16 or the response of subjects with an hSBA titer ≥ 1 : 8 at baseline who then achieved a ≥ 4-fold increase in hSBA titer. Non-inferiority criterion met.

Booster response

MET56 compared the immunogenicity of a booster dose of MenQuadfi to a booster dose of MenACWY-DT in participants aged 15 years or older and primed with a quadrivalent meningococcal conjugate vaccine (MenACWY-CRM (11.3 % of participants) or MenACWY-DT (86.3 % of participants)) 4 to 10 years previously.

At baseline, hSBA seroprotection rates and GMTs were comparable for serogroups A, C, W and Y.

Table 9: 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)

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.

** The response of subjects with an hSBA titer < 1 : 8 at baseline who then achieved an hSBA titer ≥ 1 : 16 or the response of subjects with an hSBA titer ≥ 1 : 8 at baseline who then achieved a ≥ 4-fold increase in hSBA titer. Non-inferiority criterion met.

Pharmacokinetics

Absorption

Not applicable.

Distribution

Not applicable.

Metabolism

Not applicable

Elimination

Not applicable.

Preclinical data

Non-clinical safety data revealed no special risks for humans based on a repeat-dose toxicity and local tolerance study in rats and a developmental and reproductive toxicity study in rabbits. MenQuadfi administered 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.

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Store in the refrigerator (2-8 °C).
Do not freeze.
Store in the original packaging.

Instructions for handling

The vaccine should be inspected visually for any particulate matter and/or variation of physical aspect (or discoloration) 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.

Authorisation number

68221

Packs

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 dose (0.5 mL) vials.

Marketing authorisation holder

sanofi-aventis (suisse) sa, 1214 Vernier

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