Module 1.8.2

European Union Risk Management Plan (EU-RMP) for *Menveo* (Meningococcal groups A, C, W-135 and Y conjugate vaccine)

RMP version to be assessed as part of this application	
RMP Version number	11.1
Data lock point for this RMP	14 March 2023
Date of final sign off	Please refer to the QPPV signature below.

Rationale for submitting an updated RMP

With the submission of this RMP update, the Company is proposing the following change:

- The addition of children 2-9 years of age in Part II Module SIV 'population not studied in clinical trials' for *Menveo* liquid.

Summary of significant changes in this RMP:		
PART	**MODULE**	**Changes made in EU-RMP version 11.1**
II	SI.1	Update of the incidence and prevalence section as of October 2023
II	SIV.3	Update to include children 2-9 years of age as population not studied in clinical trials for *Menveo* liquid
II	SV	Update to add that Menveo liquid is approved in Australia.
II	SVII.2 and SVII.3.2	Update to remove 'Lack of data in children 2-9 years of age' as Missing Information
II	SVIII	Updated to reflect the new list of safety concerns
V	V.1	Updated to remove the missing information 'Lack of data in children 2-9 years of age'
VI	II.A	Updated to reflect the new list of safety concerns

Other RMP versions under evaluation		
RMP Version number	**Submitted on**	**Procedure number**
NA	NA	NA

Details of the currently approved RMP		
Version number	Approved with procedure	Date of approval (opinion date)
10.0	EMEA/H/C/001095/II/0112	27 October 2022

QPPV Name	Dr. Jens-Ulrich Stegmann, MD Senior Vice President, Head of Clinical Safety & Pharmacovigilance and EU QPPV
QPPV Signature	

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PART I: PRODUCT OVERVIEW

Table 1 Product Overview

Active substance(s) **(INN or common name)**	Meningococcal groups A, C, W-135 and Y conjugate vaccine (*Menveo*)
Pharmacotherapeutic group(s) (ATC Code)	J07AH08
Marketing Authorisation Holder/ Applicant	GlaxoSmithKline Vaccines, S.r.l., a company of GlaxoSmithKline Biologicals S.A.
Medicinal products to which this RMP refers	Meningococcal groups A, C, W-135 and Y conjugate vaccine
Invented name(s) in the European Economic Area (EEA)	*Menveo*
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: Biological/Biotechnological
	Summary of mode of action: *Menveo* is a vaccine designed to prevent invasive disease caused by serogroups A, C, W-135 and Y of *N. meningitidis*. It is a protein conjugate vaccine, with purified oligosaccharides for the four serogroups chemically conjugated to a protein carrier molecule, CRM_{197}. CRM_{197} is a naturally occurring, non-toxic mutant of diphtheria toxin that has been used in the construction of several other conjugate vaccines including the seven valent pneumococcal conjugate vaccine (*Prevnar*). Immunisation with *Menveo* is intended to induce generation of bactericidal antibodies. These are antibodies capable of triggering complement-mediated cell lysis of *N. meningitidis* bacteria in vivo.
Reference to the Product Information	Please refer to the approved Product Information (see Annex 7)

Indication(s) in the EEA	Current (if applicable): *Menveo* is indicated for active immunisation of children (from 2 years of age), adolescents and adults at risk of exposure to *N. meningitidis* groups A, C, W- 135 and Y, to prevent invasive disease. The use of this vaccine should be in accordance with official recommendations.
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current (if applicable): *Children (from 2 years of age), adolescents and adults*: *Menveo* should be administered as a single dose (0.5 mL). *Elderly*: There are limited data in individuals aged 56-65 years and there are no data in individuals aged >65 years. *Booster vaccination*: Long term antibody persistence data following vaccination with *Menveo* are available up to 5 years after vaccination. *Menveo* may be given as a booster dose in subjects who have previously received primary vaccination with *Menveo*, other conjugated meningococcal vaccine or meningococcal unconjugated polysaccharide vaccine. The need for and timing of a booster dose in subjects previously vaccinated with *Menveo* is to be defined based on national recommendations. *Method of administration: Menveo* is given as an intramuscular injection, preferably into the deltoid muscle. It must not be administered intravascularly, subcutaneously or intradermally. Separate injection sites must be used if more than one vaccine is being administered at the same time.
	Proposed (if applicable): Not applicable

Pharmaceutical form(s) and strengths	Current : Powder and solution for solution for injection (*Menveo* lyo-liquid). The powder is a white to off-white cake. The solution is a colorless clear solution. Each dose (0.5 mL) of *Menveo* contains the following active ingredients: • Meningococcal group A oligosaccharide 10 µg conjugated to *Corynebacterium diphtheriae* CRM_{197} protein 16.7 to 33.3 µg • Meningococcal group C oligosaccharide 5 µg conjugated to *Corynebacterium diphtheriae* CRM_{197} protein 7.1 to 12.5 µg • Meningococcal group W-135 oligosaccharide 5 µg conjugated to *Corynebacterium diphtheriae* CRM_{197} protein 3.3 to 8.3 µg • Meningococcal group Y oligosaccharide 5 µg conjugated to *Corynebacterium diphtheriae* CRM_{197} protein 5.6 to 10.0 µg
	Proposed : Solution for injection (*Menveo* liquid). The solution is a colorless clear solution. *Menveo* liquid contains the same amounts of each antigen as *Menveo* powder and solution for solution for injection.
Is/will the product be subject to additional monitoring in the EU?	No

Abbreviations

AE	Adverse event
ADR	Adverse drug reaction
AIDS	Acquired Immune Deficiency Syndrome
AR	Annual report
aRMM	additional Risk Minimisation Measure
CBER	Center for Biologics Evaluation and Research
cc11	clonal complex 11
CDP	Clinical Development Plan
CHMP	Committee for Medicinal Products for Human Use
CRM197	Cross-Reacting Material 197
CSR	Clinical study report
CT	Clinical Trial
DLP	Data Lock Point
eCTD	electronic Common Technical Document
ED	Emergency Department
EDD	Estimated Due Date
EEA	European Economic Area
EMA	European Medicines Agency
EOI	Events Of Interest
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
FS	Free Saccharides
GLP	Good laboratory practices
GSK	GlaxoSmithKline
GSKMQ	GSK MedDRA Query
GVP	Good Pharmacovigilance Practice
HCG	Human Chorionic Gonadotropin
HCP	Health Care Provider
HMO	Health Maintenance Organisation
HIV	Human Immunodeficiency Virus
HLT	High Level Term
hSBA	human Serum Bactericidal Assay
ILI	influenza like illness
IMD	Invasive Meningococcal Disease
MAH	Marketing Authorisation Holder
MCMs	Major Congenital Malformations
MedDRA	Medical Dictionary for Regulatory Activities
MenACWY	Meningococcal A, C, W-135, Y vaccine, used in clinical development phases
Menveo lyo-liquid	*Menveo* powder and solution for solution for injection
Menveo liquid	*Menveo* solution for injection
Menveo	both *Menveo* Lyo-liquid and *Menveo* liquid
N. meningitidis	*Neisseria meningitidis*
PMS	Post-Marketing Surveillance
PRAC	Pharmaceutical Risk Assessment Committee
PSUR	Periodic Safety Update Report

PBRER	Periodic Benefit Risk Evaluation Report
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
RMM	Risk Minimisation Measure
RMP	Risk Management Plan
RSI	Reference Safety Information
SAB	Spontaneous Abortion
SAC	Scientific Advisory Committee
SAE	Serious Adverse Event
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SmPC	Summary of Product Characteristics
SR	Spontaneous report
TTO	Time To Onset
UK	United Kingdom
URI	Upper Respiratory Infection
US	United States
VAERS	Vaccine Adverse Event Reporting
System WHO	World Health Organization

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
Menveo
Bexsero
Boostrix

Trademarks not owned by the GlaxoSmithKline group of companies
Prevenar
Menactra

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Indication

Menveo is indicated for active immunisation of individuals from 2 years of age (children), adolescents and adults for the prevention of Invasive Meningococcal Disease (IMD) caused by *Neisseria meningitidis* groups A, C, W-135 and Y.

Incidence

In the EU, an overall IMD notification rate is 0.1 cases per 100 000 population in 2021, which was the lowest it has been since 2017. The notification rate decreased by 83.3% in 2021 compared with 2017 to 2019 (0.6 cases per 100 000 population). By country, notification rates ranged from zero cases (Bulgaria, Cyprus, Finland, Greece, Iceland, Italy and Liechtenstein) to 1.6 cases per 100 000 population (Malta). The highest notification rates were observed in Malta (1.6/100 000), Lithuania and Slovakia (0.4/100 000). IMD incidence was highest among the youngest age groups. The notification rate was 3.2 confirmed cases per 100 000 population in infants (under one year of age) and 0.6 confirmed cases per 100 000 population in children one to four years old. The notification rate in 15–24-year-olds (0.2 per 100 000 population) was slightly higher than in 5–14-year-olds (0.1 per 100 000 population). (ECDC, 2023).

Incidence in other regions of the world varies. Highest incidence rates were observed in the African meningitis belt, an area extending from Senegal to Ethiopia. The incidence observed during explosive epidemics in this region can exceed 1000 cases per 100 000 population (WHO, 2019). The lowest incidence rates were observed in Asia. In the US, the overall incidence rate of IMD observed in 2021 0.06/100 000 (CDC, 2023). The incidence rate of IMD caused by ACWY from 2012 to 2021 was highest among infants less than one year old (0.23/100 000), children 1-4 years old (0.07/100 000) and older adults aged 65 and above (0.10/100 000).

Prevalence

The gram-negative bacterium *Neisseria meningitidis* causes meningococcal disease, primarily meningitis and septicaemia. Multiple serogroups, including groups A, B, C, X, Y, Z, 29-E and W-135, are associated with *N. meningitidis* strains known to cause invasive meningococcal

disease. Each group is defined by chemically and immunologically distinctive polysaccharides.

Serogroup prevalence varies with geography, calendar time, and subject age group. In Europe, the dominating serogroups in 2021 were serogroup B (64%), W (12%), C (10%) and Y (7%) (ECDC, 2023). Serogroup C was most common in 5–14-year-olds while Serogroup Y was most common in 14–24-year-olds and serogroup W was most common in the 65 years and above. The notification rates of serogroups C and W both decreased to 0.01 cases per 100 000 population in 2021, compared with 0.1 cases per 100 000 population in 2017. While the notification rate of serogroup Y remained similar to the those of serogroups C and W between 2017 and 2020, a decrease to 0.010 cases per 100 000 population was observed in 2021 following the introduction of immunisation programmes across European countries in 2018 (Nuttens, 2022).Serogroup W, the second most common serogroup, had the highest notification rates in young children (under four years old) and in those 65 years and above. In 2021, serogroup C continued to have the highest case fatality rate and was the second most common cause of IMD in individuals aged 15 years old and below.

Similar to Europe, the most common serogroups observed in the US are also serogroup B, C, W and Y (CDC, 2023). Serogroup A has been the cause of repeated epidemics in sub-Saharan countries of Africa known as the African meningitis belt. Serogroup W-135 outbreaks have been reported in conjunction with travel associated with the Hajj in Saudi Arabia and W-135 has also been reported as a cause of disease in the African meningitis belt (Stephens, 2007; Decosas, 2002).

SI.1.1 Demographics of the population in the authorised indication and risk factors for the disease:

Menveo is indicated for active immunisation of children, adolescents, and adults from 2 years of age and above to prevent invasive meningococcal disease (IMD) caused by *N. meningitidis* serogroups A, C, W-135 and Y. Selection of vaccine is made according to national vaccination programmes which in most cases recommend vaccination with quadrivalent meningococcal vaccines of individuals aged 10 to 20 years.

Risk factors for the disease

The incidence of meningococcal disease is influenced by the maturation of the human immune response and the variable susceptibility of individuals at different ages. Neonates are relatively protected against developing meningococcal disease as a result of passive acquisition of transplacental maternal antibodies. As infants age, their levels of maternal antibodies decrease, and they become more susceptible to meningococcal disease. The lowest antibody levels are found in infants between 6 months and 2 years of age; natural immunity begins to be acquired after 2 years of age (Pollard, 2001; Goldschneider, 1969a; Goldschneider, 1969b). Meningococcal disease is, therefore, predominantly a disease of infants and young children, although increased disease incidence can also occur in adolescents and adults. Examples of the latter include epidemics among military recruits during basic training and increased meningococcal disease rates among college students residing in dormitories (Goldschneider, 1969a; Goldschneider, 1969b; Bruce, 2001; CDC, 2013) largely determined by overcrowding and risk factors associated with social behaviour. Waning immunity among a population against a particular strain favours epidemics, as do high incidence of upper respiratory tract infections and climatic conditions such as dry seasons or prolonged drought and dust storms. Underlying

immune defects that confer a predisposition to invasive meningococcal infection include functional or anatomical asplenia, properdin deficiency, a deficiency of terminal complement components and HIV infections.

SI.1.2 The main existing treatment options

Meningococcal disease is potentially fatal and should always be viewed as a medical emergency. Admission to a hospital or health centre is necessary, although isolation of the patient is not necessary. Appropriate antibiotic treatment must be started as soon as possible, ideally after the lumbar puncture if the procedure can be performed immediately. If treatment is started prior to the lumbar puncture, it may be difficult to culture the bacterium from the spinal fluid and thus to confirm the diagnosis.

A range of antibiotics can treat meningococcal infection, including penicillin, ampicillin, chloramphenicol and ceftriaxone. Under epidemic conditions in Africa in areas with limited resources and health infrastructure, oily chloramphenicol or ceftriaxone are the drugs of choice because a single dose has been shown to be effective against meningococcal meningitis.

SI.1.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

Patients with invasive meningococcal infection often present initially with fever, and influenza like illness (ILI). Symptoms can rapidly progress to include signs of meningism (stiff neck, severe headache, vomiting, and photophobia) and meningococcaemia (purpura, petechiae, hypotension, cyanosis, seizures), and can result in multiple organ dysfunction. Within a few hours, otherwise healthy individuals can be permanently disabled or disfigured or die of the disease.

Despite the availability of medical treatment and effective antibiotics, 9-10% of invasive meningococcal disease patients in the industrialized countries die, increasing with age (ECDC, 2019a, Ladhani, 2012, Harrison, 2010) and up to 10-19% of survivors have lifelong sequelae (Kirsch, 1996, Edmond, 2010), including hearing loss, speech disorders, loss of limbs, mental retardation, paralysis, and skin scarring.

SI.1.4 Important co-morbidities

Menveo, as most of the prophylactic vaccines, is intended for the general population (from 2 years of age) and does not target a specific population who receive specific treatments that could be frequently used concomitantly. It is expected that the subjects could receive concomitant vaccination.

As noted in the WHO Guidelines on Nonclinical Evaluation of Vaccines (2005), pharmacokinetic testing is not required for final vaccine formulations.

No interaction linked to the metabolism is expected with vaccines. The only potential for interaction is with other vaccines administered concomitantly and with immunosuppressing drugs.

The AE, ADR and SAE profiles from the Clinical Development Plan (CDP) did not reveal any identified or potential food and drug interactions. While the studies were not designed to have power to detect interactions with food or drugs, many study subjects were taking certain

medications that were deemed not to disqualify them for study, and among these subjects, there was no report of suspected drug interaction. Studies V59P11 and V59P18 demonstrated no increase in local reactogenicity when *Menveo* powder and solution for solution for injection (hereafter referred to as *Menveo* lyo-liquid) was administered concomitantly with Tdap vaccine or vice versa. Study V59P18 also analysed the sequential administration of *Menveo* lyo/liquid and Tdap and similarly found no increase in local or systemic reactogenicity.

Study V59_40 demonstrated higher frequencies of local and systemic solicited adverse events (AEs) after the first study vaccination when *Menveo* lyo-liquid was administered concomitantly with Tdap and HPV, versus when Tdap and HPV were coadministered without *Menveo* (local AEs: 54% vs. 43% respectively; systemic AEs: 53% vs. 46% respectively).

Study V72_56 evaluated the safety and the tolerability of *Bexsero* and *Menveo* when concomitantly administered at 3, 5, 7 and 13 months of age, compared to either alone. Overall, no increase in local and solicited AEs was observed after the concomitant administration of *Bexsero* and *Menveo* vaccines compared with administration of each vaccine alone, and there was no increase in reactogenicity with the subsequent doses.

PART II: MODULE SII - NONCLINICAL PART OF THE SAFETY SPECIFICATION

The nonclinical safety assessment program was designed based on appropriate global regulatory requirements for testing of vaccines and adjuvants, and for *Menveo* to support the clinical administration of single and multiple intramuscular injections of the vaccine in adolescents and adults (11 and older), children (2-10 years of age), as well as infants/toddlers (2-23 months).

Studies such as secondary pharmacology, safety pharmacology, pharmacokinetics (absorption, distribution, metabolism, or excretion) or toxicokinetic studies were not conducted, as they are not required for vaccines, in line with the applicable WHO 2005 guideline.

The *Menveo* nonclinical package consisted of both pharmacology (immunogenicity) and toxicology studies. The immunogenicity studies were conducted in mice to evaluate formulations with and without adjuvants and monovalent versus tetravalent combinations. The toxicology studies investigated general toxicology, local tolerability, and reproduction and embryofetal development toxicity in rabbits. All toxicology studies were conducted using 1× and 2× the clinical dose and the clinical route of administration (intramuscular). Alum-adjuvanted MenACWY formulations (either as aluminum hydroxide or aluminum phosphate) and non-adjuvanted formulations were used in these toxicology studies.

Five Good Laboratory Practice (GLP) toxicology studies were conducted. A single- and repeat-dose (5 doses) toxicology study was conducted in rabbits to assess the systemic toxicity and local tolerability of GSK MenACWY formulation adjuvanted with $AlPO_4$ or $Al(OH)_3$. Two repeat-dose (2 doses) toxicology studies were conducted in rabbits to assess the systemic toxicity and local tolerability of GSK non-adjuvanted MenACWY formulation. A GLP pilot reproductive and developmental toxicity study (embryofetal development) was conducted in rabbits to assess the maternal toxicity and teratogenic potential of $AlPO_4$ adjuvanted and non-adjuvanted GSK MenACWY. A GLP pivotal reproductive and developmental toxicity study, including postnatal evaluation, was also conducted with non-adjuvanted GSK MenACWY in rabbits to evaluate any effect on maternal toxicity and female reproduction, embryofetal toxicity and offspring development. The results of these studies are summarized below.

The GLP general rabbit toxicology studies demonstrated that one or five multiple administrations of adjuvanted or two doses of non-adjuvanted MenACWY were locally and systemically well-tolerated. In the first study, one or five doses of adjuvanted MenACWY showed changes consistent with an inflammatory reaction (at a slightly higher incidence/severity in the adjuvanted MenACWY treated animals) following intramuscular vaccination and reversibility of findings seen at the injection sites was observed for all study animals. The other two general toxicology studies showed that two doses of non-adjuvanted MenACWY administered intramuscularly to rabbits were immunogenic and well-tolerated both locally and systemically. On a microgram per kilogram basis, rabbits (approximately 4 kg) administered two 25 µg doses of MenACWY vaccine received approximately 10× the dose to an adolescent, assuming a 40 kg human body weight.

The GLP rabbit reproductive toxicology studies demonstrated that there were no effects on embryofetal development in the pilot dose ranging study in rabbits when 1× or 2× the clinical

dose of adjuvanted and non-adjuvanted MenACWY were administered three times pre-gestation and twice during gestation. There were no effects on reproduction, embryofetal and postnatal development in the GLP pivotal rabbit study when 1× the clinical dose of non-adjuvanted MenACWY was administered three times pre-gestation and twice during gestation, thus representing, on a body weight basis, approximately 10× the human dose and an excess by two to four administrations versus the planned clinical regimen. MenACWY was immunogenic in maternal rabbits and the fetuses had titers comparable to their mothers; in F1 offspring antibodies persisted through the first 4 weeks of life.

Key safety findings from nonclinical studies and relevance to human usage:

Key Safety findings (from nonclinical studies)	Relevance to human usage
Toxicity including: • Repeat Dose Toxicity: Findings consistent with inflammatory changes expected following vaccination; reversible inflammation reactions at the injection sites; • Reproductive Toxicity: No test article-related maternal findings during reproduction and pregnancy; • Developmental Toxicity: No embryofetal and developmental effects related to the test article.	• *Menveo* administration resulted in expected findings consistent with inflammatory changes following vaccination, of mild severity and limited duration; local reactogenicity rates comparable with licensed comparators (e.g., *Menactra, Boostrix*) in severity and of limited duration • No expectation of maternal safety risk; • Safety risk not anticipated for embryos, fetuses and lactating newborns.
General Safety pharmacology:	Not applicable in alignment to WHO 2005
Other toxicity-related information or data (as applicable)	None

No need for additional nonclinical data has been identified.

In conclusion, for the nonclinical part of the safety specification: no safety concerns were identified in nonclinical studies that would be considered relevant for use in humans.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Menveo is currently available as a 2-vial or a 1-vial presentation:

- *Menveo* lyo-liquid is presented in two vials: one vial contains the lyophilised MenA conjugate component, and one vial contains the liquid MenCWY conjugate component.
- *Menveo* liquid is presented in a single ready-to-use vial that contains the liquid MenACWY conjugate components.

Safety and immunogenicity of *Menveo* lyo-liquid were evaluated in individuals aged 2 years and older in the following phase 2 and phase 3 studies: V59P6, V59P6E1, V59P7, V59P8, V59P10, V59P11, V59P13, V59P13E1, V59P17, V59P18, V59P20, and V59P20E1. These studies established non-inferior immunogenicity of a single dose of *Menveo* versus licensed comparators, safety in a large population, lot-to-lot consistency, concomitant administration with routine adolescent vaccinations and traveler vaccines, persistence of antibody response up to 5 years and response to a booster dose. The safety and immunogenicity of *Menveo* lyo-liquid in subjects between the ages of 2 months and 23 months were assessed in studies V59P5, V59P8, V59P7, V59P9, V59P14, V59P14E1, V59P16, V59P21, V59P22, V59_33 and V59_36. In addition, study V59P23 provided safety data only. Study V59P14 was the pivotal infant immunogenicity study, while V59P23 was the pivotal infant safety study. StudyV59_33, completed in 2012, is also considered pivotal study for immunogenicity. These studies established sufficient immunogenicity of a primary 4-dose schedule or an alternative 3-dose schedule in infants, and 1 or 2 catch up doses for unvaccinated toddlers. These studies also established safety of multiple vaccinations in a large population, as well as concomitant administration with routine infant vaccines, and antibody persistence up to 5 years and response to a booster dose.

To simplify the vaccine administration and prevent administration errors, a fully liquid (solution) presentation of *Menveo* has been developed (*Menveo* liquid) in a single ready-to-use vial. This liquid (solution) presentation contains the same amount of meningococcal serogroups A, C, W and Y oligosaccharides conjugated to CRM197 protein as the ones included in *Menveo* lyo-liquid. The main qualitative and quantitative differences between the two formulations are that serogroup A component is liquid and not lyophilized and therefore the sucrose and potassium phosphate (used as lyophilization matrix of MenA conjugate component of *Menveo* lyo-liquid) are absent in *Menveo* liquid.

The indication proposed for *Menveo* liquid is identical to that of *Menveo* lyo-liquid, i.e., active immunisation to prevent invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, W-135 and Y.

Two Phase 2b clinical studies were conducted to evaluate the immunogenicity and safety of *Menveo* liquid, aged either artificially for approximately 2 months or naturally for 24 and 30 months, to clinically validate MenA Free Saccharides (FS) and O-acetyl specifications (study V59_71) and the shelf-life (study V59_78) of the liquid vaccine presentation. The safety and reactogenicity data from studies V59_71 and V59_78 and the pooled analysis showed that the safety profile for *Menveo* liquid is very similar to that of *Menveo* lyo-liquid (Vandermeulen, 2021; Díez-Domingo, 2021; Vir Singh, 2023).

Clinical Trial Exposure

The cumulative clinical trial exposure data includes not only subjects who received *Menveo* (lyo-liquid and liquid) in completed trials in the CDP but also subjects participating in studies in which *Menveo* lyo-liquid formulation was used as comparator in other CDPs.

As of 14 Mar 2023 the estimated total exposure of clinical trial subjects to *Menveo* in GSK studies was 37,754 (Open label/unblinded) subjects.

Estimates of overall cumulative subject exposure are provided in Table 2, based upon actual exposure data from completed studies and the enrolment/randomization schemes for ongoing studies. Studies that included MenACWY lyo-liquid early formulations that were not brought forward into development as part of a protocol-specified baseline therapy are not included in Table 2.

Table 2 Subject exposure to *Menveo* in GSK studies*

	Completed** and Ongoing Open-Label Studies N=50591	Ongoing*** Blinded Studies N=7388	Total N=57979
	n	N	n
Vaccination in *Menveo* CDP			
Menveo liquid	1339§	0	1339
Menveo lyo-liquid	35066	0	35066
Other Comparators	10570	0	10570
Placebo	164	0	164
Vaccination in other CDP where *Menveo* is co-administered or used as comparator			
Blinded	0	7388§§	7388
Menveo lyo-liquid as comparator	1349	0	1349
Non-MenACWY Groups	2023	0	2023
Placebo	80	0	80

CDP= Clinical Development Plan
N=total number of subjects
Data Lock Point (DLP) is 14 MARCH 2023
*Includes subjects who received *Menveo* as part of study protocol at the DLP
**Studies completed at the DLP
***Includes blinded studies whose study report finalisation is planned after DLP
§ Two subjects (one each from the 2 *Menveo* liquid studies) were later found to have issues with their ICF (Informed Consent Form) and were thus excluded from the respective clinical study reports. However, these were taken into consideration while calculating the overall exposure for *Menveo* liquid until the DLP.
§§ Study 212458 (MENACWY=MEN7B-001 PRI) presents a one open label arm in Phase II where both *Bexsero* and *Menveo* are administered. However, since the other arms in Phase II are blinded, exposure data is overall presented as blinded.

An estimate of cumulative exposure to *Menveo* by age and sex for ongoing open-label and completed clinical trials is provided in Table 3.

Table 3 Cumulative Estimate of Subject Exposure to *Menveo from Ongoing Open-Label or Completed Clinical Trials by Age and Sex****

	M N=17875	F N=19879	Total N=37754
	N	n	N
Age range			
< 1 year	6339	6170	12509
1-<2 years	1406	1294	2700
2-<3 years	427	413	840
3-<6 years	1124	1108	2232
6-<11 years	1213	1229	2442
11-<18 years	3577	3349	6926
≥ 18 years	3789	6316	10105
Not Available	0	0	0

* Includes both *Menveo* liquid and *Menveo* lyo-liquid formulations
** Data Ongoing Open-Label or Completed Clinical Trials as of 14 March 2023
Note: This table includes subjects who received *Menveo* as part of study protocol during completed or ongoing open-label studies only. Subjects exposed to *Menveo* in blinded ongoing studies are not included in this table.

An estimate of cumulative exposure to *Menveo* by racial group for completed clinical trials is provided in Table 4.

Table 4 Cumulative Estimate of Subject Exposure to *Menveo from Ongoing Open-Label or Completed Clinical Trials by Racial Group****

	Total N=37754
	n
Geographic Ancestry	
AMERICAN INDIAN OR ALASKA NATIVE	23
ASIAN	6290
BLACK OR AFRICAN AMERICAN	2172
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	10
WHITE	27015
OTHER	2244
UNKNOWN	0

* Includes both *Menveo* liquid and *Menveo* lyo-liquid formulations
** Data Ongoing Open-Label or Completed Clinical Trials as of 14 March 2023
Note: This table includes subjects who received *Menveo* as part of study protocol during completed or ongoing open-label studies only. Subjects exposed to *Menveo* in blinded ongoing studies are not included in this table.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Note: For the purposes of this RMP, the data provided in this section pertain only to subjects 2 years of age and older.

In the *Menveo* CDP, the safety population was defined as the set of subjects exposed to study vaccine who provided any safety data. As is typical for vaccine trials, a limitation of the human safety database for *Menveo* is that enrollment was limited to otherwise healthy subjects, based on medical history, physical examination, and the clinical judgment of the investigator. Subjects were ineligible for the studies if they had: any serious chronic or progressive disease (e.g., any history of neoplasm, insulin dependent diabetes mellitus, cardiac disease, autoimmune disease, human immunodeficiency virus infection or other acquired immunodeficiency syndrome, blood dyscrasias, cardiac or renal failure, or severe malnutrition); epilepsy or any progressive neurological disease; history of any anaphylactic shock, pulmonary reactivity, urticaria, or other allergic reaction after previous vaccinations or hypersensitivity to any vaccine component; known or suspected disease of the immune system, who were receiving immunosuppressive therapy, including use of any immunosuppressive doses of systemic corticosteroids; taken systemic antibiotics (either oral or parenteral) within the previous 7-14 days; a bleeding diathesis or any condition that may have been associated with a prolonged bleeding time; Down syndrome or other known genetic disorder.

Pregnant women were restricted from enrollment, and though a small number did become pregnant during studies in the dossier, data from these subjects provided insufficient information by which to judge the safety or risk of *Menveo* use during pregnancy.

Similarly, subjects with chronic diseases, those receiving immunosuppressants or immunostimulants, or other medications that were perceived to have a risk of impairing the immune response to *Menveo*, or which might obscure an effect that was induced (such as individuals who received pooled antibodies for any reason, and thus might have antibodies that were exogenous, rather than being induced by the vaccine), were excluded from enrollment.

Lastly, because the trials sought to demonstrate the immunogenicity of the experimental vaccine (*Menveo*), individuals with previous *N. meningitidis* infection were restricted, as well as individuals previously vaccinated with other meningococcal vaccines (except for booster studies in which *Menveo* and other meningococcal vaccines, according to the study design, were administered to healthy individuals approximately from 1 to 6 years after primary ACWY vaccination).

Limited immunogenicity and safety data exist among subjects between 56 and 65 years of age; minimal clinical data exist for subjects over 65 years of age.

The clinical trials in the CDP were not designed to assess for a differential effect of the vaccine among subpopulations with different genetic or ethnic backgrounds. Likewise, there have been no clinical trials conducted in subjects with co-morbidities or immune deficiencies, as this vaccine is intended for use in the general population.

At present, there are no data regarding the immunogenicity or safety of repeated initial vaccinations with *Menveo* within the 11 year and above age group.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rational
Hypersensitivity to the active substances or to any of the excipients of the vaccine.	The vaccine must not be administered to individuals with hypersensitivity to the active substances	No	Included in SmPC Section 4.3, 'Contraindications' and in Section 4.8, 'Undesirable effects'.
Current or previous, confirmed, or suspected disease caused by *N. meningitidis*.	The evaluation of vaccine immunogenicity would have been impacted if a subject previously had been naturally primed with A,C,W,Y antigens; thus, these subjects were excluded from enrolling.	No	There is still a benefit to vaccinate subjects who previously had meningococcal infection as they might not be protected against all strains.
Serious acute illness with fever	Drug class-related potential safety concern. Causality assessment of adverse events would have been complicated by inclusion of subjects with preexisting illness, for this reason, serious acute illness with fever was a temporary exclusion condition for the vaccination visits.	No	Included in SmPC Section 4.3 'Contraindication': 'As with other vaccines, *Menveo* should be postponed in individuals suffering from an acute severe febrile illness. The presence of a minor infection is not a contraindication'.
Autoimmune disorders	Autoantibodies in sera might have had an adverse impact on serological testing of the vaccine as these antibodies are often cross-reactive to foreign antigens.	No	Known safety profile does not warrant exclusion of these populations

Immunodeficient conditions, including AIDS	If *Menveo* is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the expected immune response may not be obtained.	No	It is not a contraindication as this population vulnerable to infection might benefit of the vaccination. A special warning and precaution for use is included in the SmPC Section 4.4 'Special warnings and precautions for use': 'In immunocompromised individuals, vaccination may not result in an appropriate protective antibody response. While Human Immunodeficiency Virus (HIV) infection is not a contraindication, *Menveo* has not been specifically evaluated in immunocompromised people. Individuals with complement deficiencies and individuals with functional or anatomical asplenia may not mount an immune response to meningococcal group A, C, W135 and Y conjugate vaccines. Individuals with familial complement deficiencies (for example, C3 or C5 deficiencies) and individuals receiving treatments that inhibit terminal complement activation (for example, eculizumab) are at increased risk for invasive disease caused by *N. meningitidis* group A, C, W-135 and Y, even if they develop antibodies following vaccination with *Menveo*'.
History of neoplasia	Vaccine immunogenicity in these individuals is not known but could potentially be lower than in the healthy population, as neoplasia is	No	Known safety profile does not warrant exclusion of these populations.

	sometimes associated with anergy.		
Serious chronic or progressive disease (cardiac, renal, diabetes, severe malnutrition)	The vaccine's safety profile in this population could be complicated to establish since it would be difficult to differentiate the onset of a new adverse reaction with the progression of a pre-existing chronic condition.	No	Known safety profile does not warrant exclusion of these populations.
Blood dyscrasias	*Menveo* has not been evaluated in persons with thrombocytopenia, bleeding disorders or that are receiving anticoagulant therapy, because of the risk of hematoma.	No	Included in SmPC Section 4.4 'Special warning and precaution for use': '*Menveo* has not been evaluated in persons with thrombocytopenia, bleeding disorders or that are receiving anticoagulant therapy, because of the risk of hematoma. The risk-benefit ratio for persons at risk of hematoma following intramuscular injection must be evaluated by health care professionals'.
Epilepsy, any progressive neurological disease, or history of Guillain-Barré Syndrome (GBS)	Potential confounder in safety analyses of clinical trials.	No	Following vaccination with a US licensed meningococcal quadrivalent polysaccharide conjugate vaccine (*Menactra*), an evaluation of post marketing adverse events suggested a potential for an increased risk of Guillain-Barré syndrome (GBS); however, no data from post-marketing use of *Menveo* or from clinical trials suggest an association between *Menveo* and GBS and for this reason is not contraindicated.

Down syndrome or other known cytogenic disorders	Potential confounder in safety analyses of clinical trials.	No	Known safety profile does not warrant exclusion of these populations.
Pregnant women	General potential safety concern.	No	Included in SmPC Section 4.6 'Fertility, pregnancy and lactation': 'Insufficient clinical data on exposed pregnancies are available. In nonclinical studies, *Menveo* had no direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition, or postnatal development. Considering the severity of invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, W135 and Y, pregnancy should not preclude vaccination when the risk of exposure is clearly defined'.
Children younger than 55 days of age	The immunogenicity of a polysaccharide conjugated vaccine in very young infants might not be optimal, due to immaturity of the immune system at this age.	No	*Menveo* is not indicated for the use in this population.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Table 5 Limitations of ADR detection common to clinical trial development programmes

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare	37,754 subjects were exposed over the whole CT programme of *Menveo.*	ADRs with a frequency greater than 1 in 12,585 could be detected if there were no background incidence for *Menveo*.
Due to prolonged exposure	There is no prolonged exposure with prophylactic vaccines.	NA
Due to cumulative effects	There is no cumulative exposure nor specific organ toxicity that has been observed with *Menveo*.	NA
Which have a long latency	There is no potential or identified risk that could have a long latency following vaccination with *Menveo*.	NA

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

- **Special age groups**

Children

Children born pre-term have not been studied due to incomplete development of the immune system for several months after the birth; no trials in children born pre-term are planned.

Infants 55 days of age and younger also have not been studied, due to incomplete development of the immune system and known poorer vaccine responses to polysaccharide vaccines. Of note, as a result of protocol deviations, 51 subjects aged 44-54 days were inadvertently enrolled in these studies and received at least one dose of *Menveo*.

There are no data on the use of *Menveo* liquid in subjects 2-9 years of age (children) since no clinical trials have been performed in this age group. However, like in individuals 10 to 40 years of age, the improved liquid formulation is not expected to behave differently from Menveo lyo-liquid in children below 10 years of age, considering:

- the minimal changes to the vaccine formulation. The main qualitative and quantitative differences between the *Menveo* liquid and *Menveo* lyo-liquid are the absence of sucrose and potassium phosphate that were added as lyophilisation matrix of MenA conjugate

component in *Menveo* lyo-liquid. Further details in Part II Module SIII.

- the percentage of MenA FS at the end of the vaccine intended shelf-life is not expected to induce any hyporesponsiveness phenomenon considering that short saccharide chains are not able to effectively cross-link B cell receptors and hence no impact on immunological response or safety is expected. In addition, assuming MenA fully acetylated at release and fully de-O-acetylated at the time of vaccine administration, the level of free acetate (2.5 µg) for an entire vaccine dose (0.5 mL), is still several orders of magnitude below the permissible daily exposure for children (around 5 mg/day [ICH, 2021]) and no detrimental effect on vaccine safety profile is expected from the release of acetate during de-O-acetylation of the MenA saccharide during storage;
- the safety and reactogenicity data from the two Phase 2b clinical trials, V59_71 and V59_78 in subjects aged 10 years and above, and the pooled analysis showed that the safety profile for *Menveo* liquid is very similar to that of *Menveo* lyo-liquid (further details in Part II Module SIII);
- the large Menveo lyo-liquid post-marketing experience demonstrates a favorable benefit-risk profile in all age groups, including the paediatric indication;
- there is evidence from the literature that fully liquid MenACWY vaccines on the market are safe and effective in individuals ≥2 years of age (Conti, 2023; Marshall, 2022).

In conclusion, the expected immunological and safety behavior of the *Menveo* liquid in subjects younger than 10 years is similar to that of the *Menveo* lyo/liquid, and no trials are planned.

Elderly

Limited immunogenicity and safety data exist among elderly subjects between 56 and 65 years of age and minimal clinical data exist for individuals over 65 years of age.

In 2015, a phase 3, multi-center, open-label study (V59_43) was conducted to evaluate the immunogenicity and safety of *Menveo* lyo-liquid in healthy Indian subjects aged 2–75 years. A single dose of *Menveo* induced a robust immune response against all four meningococcal serogroups and the safety data demonstrated that *Menveo* was well tolerated in all age groups, and no safety concerns were identified (Lalwani, 2015).

Although *Menveo* had not been studied in elderly (i.e., persons older than 65 years of age), subjects 50 years of age and older were not systematically excluded for moderate chronic renal, cardiac cardiovascular, pulmonary, rheumatic or endocrine (diabetes mellitus) conditions; these subjects were included per the judgment of the investigator.

Elderly subjects, including those with any of aforementioned chronic conditions are not expected to have higher reactogenicity to the vaccine, except possibly for the following: bruising at injection site due to fragile peripheral blood vessels; and questionably worse malaise, fatigue, myalgia and arthralgia due to ongoing comorbid conditions. Elderly individuals with chronic comorbidities are also often receiving medication on a permanent basis, however only immunomodulatory agents used for chronic rheumatic conditions, including corticosteroids, might impact immunogenicity of the vaccine.

- **Pregnant or breast-feeding women**

In *Menveo* clinical trials, pregnant women have been excluded from enrollment. Despite this requirement, a total of 56 cases of pregnancy in women participating in clinical trials and receiving *Menveo* were reported. There have been 10 spontaneous abortions with no apparent congenital anomaly, 1 ectopic pregnancy, 6 elective termination and 39 live birth infants with no apparent congenital anomaly. Of these, one spontaneous abortion was assessed by the Investigator as possibly related. This event occurred in a 34-year-old *Menveo* vaccine subject in study V59_P17, that had a negative urine human chorionic gonadotropin (HCG) test on the day of vaccination. The abortion occurred 44 days after vaccination and was estimated by HCG level to have occurred during the fourth or fifth week of pregnancy. Causality has been then excluded by the sponsor as there is no evidence from nonclinical testing, clinical trials, and post-marketing surveillance that inactivated vaccines might negatively affect pregnancies and might cause abortion.

Pregnancy outcomes in clinical trial subjects that received *Menveo* are presented in the table below.

Pregnancy outcomes in *Menveo* trials, by trial

Trial Number	Number of Pregnancies	Liveborn	Spontaneous Abortion	Therapeutic Abortion	Ectopic pregnancy
V59P13	15	10	1	4	0
V59P17	13	10	3	0	0
V59P18	9	7	2	0	0
V59_40	1	1	0	0	0
V59_43	1	1	0	0	0
V59_77	3	2	1	0	0
V72_29	1	0	0	1	0
V59_71	9	6	2	0	1*
V59_78	4	2	1	1	0
Totals	**56**	**39**	**10**	**6**	**1**

* Ectopic Pregnancy: Subject had salpingectomy.

In addition, the descriptive analysis of data reported from the *Menveo* pregnancy registry, provided safety information about inadvertent *Menveo* vaccination during pregnancy. Ninety-two (92) women received *Menveo* within 28 days prior to conception or during pregnancy, mainly during the first trimester (76.1%). Among the known pregnancy outcomes (n = 66; excluding induced abortions and unknown pregnancy outcomes), the prevalence of spontaneous abortions was 18.2% (n = 12). Among live born infants (n = 55; from 54 pregnancies), 14.5% (n = 8) were born preterm (<37 weeks gestation) and 9.1% (n = 5) had a low birthweight (<2500 g). The prevalence rate of major congenital malformations (MCMs) among live born infants (n = 55) was 1.8% (n = 1). Data from this study provided baseline prevalence estimates of spontaneous abortions, preterm births, low weight births, and MCMs among women inadvertently exposed to *Menveo* during the pregnancy period. These estimates were found to be comparable with US background prevalence estimates, and no safety issues were identified (Becerra-Culqui, 2020a).

The available data in pregnant woman in clinical interventional trials and the pregnancy registry do not highlight signals; however, these data is limited to judge the safety of *Menveo* in this population.

- **Immunocompromised individuals**

In immunocompromised individuals, vaccination may not result in an appropriate protective antibody response. *Menveo* has not been evaluated in the immunocompromised; individuals with HIV infection, complement deficiencies and functional or anatomical asplenia may not mount an immune response to meningococcal group A, C, W-135 and Y conjugate vaccines. Such subjects are routinely excluded from clinical trials due to concerns about poor immune responses in this population.

A descriptive, observational safety study (V59_74OB) was conducted as post-marketing commitment, required by the US regulatory authority, with the aim to evaluate the safety profile of *Menveo* lyo-liquid among infants and toddlers (2 to 23 months old) in the 6 months following the administration of the vaccine. Most of the 138 infants/toddlers who received *Menveo* either had a high-risk condition (i.e., anatomic/functional asplenia or DiGeorge syndrome) (42.0%), or a travel indication (54.3%). The incidence rate of emergency department (ED) visits was 0.6/person-year (95% CI: 0.5-0.8), 0.4/person-year (CI: 0.3-0.5) for hospitalisations, and 0.1/person-year (CI: 0.1-0.3) for ED to hospital transfers.

Overall, 29.0% of recipients had an incident diagnosis in the ED or hospital setting. Fever and acute upper respiratory infections were the most common diagnoses, with 46 out of 47 diagnoses occurring among infants with high-risk conditions. Data from this descriptive observational study did not suggest safety issues associated with *Menveo* lyo-liquid when used as part of clinical care of 2-23 month-old infants/toddlers indicated for vaccination (Becerra-Culqui, 2020b).

- **Patients with hepatic impairment**

Assessments of vaccine pharmacokinetics and hepatic function were not conducted in alignment with vaccine guidelines. Results of clinical laboratory testing from early phase trials in the CDP did not demonstrate evidence of a clinically relevant negative effect on hepatic function. For this reason, GSK does not anticipate that *Menveo* will exacerbate hepatic impairment or have a different safety profile in this patient population.

- **Patients with renal impairment**

As stated, assessments of vaccine pharmacokinetics were not conducted in alignment with vaccine guidelines. Results of clinical laboratory testing from early phase trials in the CDP did not demonstrate evidence of a clinically relevant negative effect on renal function. GSK does not anticipate that *Menveo* will exacerbate renal impairment or have a different safety profile in this patient population.

- **Patients with other relevant co-morbidity**

In the largest safety trial conducted in subjects 11 years of age and older, a number of subjects with a history of chronic diseases such as mild-to-moderate asthma, hypothyroidism, hypertension, psychiatric disorders (e.g., depression), and obesity were enrolled. There was no evidence of a negative effect of vaccination with *Menveo* lyo-liquid on disease control in these subjects.

- **Patients with a disease severity different from the inclusion criteria in the clinical trial population**

As stated, the CDP population was generally healthy as measured by subject history, physical exam, and clinical laboratory testing; however, individuals with mild-to moderate cases of obesity, cardiovascular, renal or endocrinologic disorders (hypothyroidism, diabetes) were enrolled and contributed to the safety database. In addition, there were subjects 2-10 years of age diagnosed while on trial with epilepsy or progressive neurologic disorders. These subjects also contributed to the safety database. In addition, various allergic conditions (environmental allergy, food allergy, or asthma were prevalent in the CDP population, either as medical history or newly diagnosed after enrollment. There was no evidence of a worsening of the condition.

- **Sub-populations carrying known and relevant polymorphisms**

Individuals with known complement deficiency, particularly those involving the alternative pathway, were excluded from study participation.

- **Patients of different racial and/or ethnic origin**

As previously stated, the *Menveo* CDP was not designed to assess the effect of the vaccine among populations with different genetic or ethnic backgrounds. In addition, the safety of the vaccine in different ethnic groups is difficult to compare if not assessed within the same country and the health system presents different approaches of medical reporting of certain events. Also, different environmental factors and different comorbidities across regions can affect the safety data consistency.

However, sub-analyses done on data from large safety trials conducted in mixed racial and ethnic groups in the same country had not shown significantly different safety profile of the vaccine in different racial groups. Despite this, multiple regional trials are currently ongoing or are completed (Korea, Taiwan) showing relative similar safety profile of the vaccine.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

GSK received its first approval of *Menveo* lyo-liquid on 19 February 2010 in the United States (US), and currently is indicated for active immunisation of infants and children from 2 months of age, adolescents and adults up to 55 years of age to prevent invasive meningococcal disease caused by the A, C, W and Y serogroups of *N. meningitidis* at dose of a single 0.5 mL intramuscular injection.

GSK received subsequently the approval of *Menveo* lyo-liquid on 15 Mar 2010 in Europe, and currently is indicated for active immunisation of children from two years of age, adolescents and adults, to prevent invasive meningococcal disease caused by the A, C, W and Y serogroups of *N. meningitidis* at dose of a single 0.5 mL intramuscular injection.

Menveo lyo-liquid is currently approved in the US, all European Economic Area (EEA) countries, the United Kingdom (UK) as well as in 27 further countries. The age indication varies based on the respective regulatory approvals with the lowest one in infants starting from two months of age.

Menveo liquid is currently approved in US (on 14 October 2022) for individuals aged 10 through 55 years, in Brazil (on 17 October 2022) for individuals from 2 months and above, and in Australia (on 26 September 2023), with an indication for active immunisation of individuals from 2 years of age.

SV.1 Post-authorisation exposure

Changes to the cumulative post-marketing exposure do not alter considerations on the risk evaluation for *Menveo*.

SV.1.1 Method used to calculate exposure

Information on the actual number of people exposed to *Menveo* in the different countries is not available to the MAH due to limited availability and the heterogeneity of data sources between and within countries (e.g. multiple national immunisation schedules, specific mass vaccination campaigns, incidence of the disease, catch-up, outbreak containment, etc.). Therefore, the patient exposure is approximated by the number of doses distributed, which is the most reliable data available with regard to patient exposure for a vaccine in a post-marketing setting.

It is important to note that the sales database from which data are retrieved is an in-house 'living' database and is subject to updates and corrections depending on information provided by GSK local country subsidiaries (e.g. vaccine doses may be returned by subsidiaries to the central warehouse). These constant updates may result in discrepancies between consecutive queries of the sales database. Sales data are available at the end of each month, but not for a date within a month. The time lag between an actual distribution to a country and recording in the database is two months on average. In order to minimise the risk of inaccuracy and to better reflect the exposure data the sales data are retrieved with EU-RMP Data Lock Point (DLP) minus two months.

SV.1.2 Exposure

Please note that sales data from the period prior to January 2011 are not available due to the integration of the Novartis sales database with the GSK sales database in 2015.

Since January 2011 until 14 March 2023, it is estimated that 78,627,732doses of *Menveo* lyo-liquid have been distributed. As vaccination with *Menveo* could vary between 1 and 4 doses per subject in accordance with local recommendations and compliance with the respective vaccination schedules, the number of subjects exposed since January 2011 until 14 March 2023, is estimated as being between 19,656,933 and 78,627,732.

Since January 2011 until 14 March 2023, 0 doses of *Menveo* liquid have been distributed, therefore no subjects were exposed to *Menveo* liquid.

Exposure by age group, gender and dose is not available from the sales database.

Part II: Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable; a meningitis vaccine is not considered as a drug with potential for abuse.

Part II: Module SVII – Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII 1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

None

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified Risk: None.

Important Potential Risk: None.

SVII.3.2 Presentation of the missing information

Missing Information: None

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PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 6 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

No routine PV activities beyond adverse reaction reporting and signal detection activities are required.

III.2 Additional pharmacovigilance activities

None.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable as there is no additional pharmacovigilance activity.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

None.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

At this stage, the Company considers that the SmPC, of which a different version for each formulation has been created, is a sufficient risk minimisation tool and that no risk minimisation activities beyond routine activities (e.g., product labeling) are needed to be planned. The Company concludes that there is no need for additional risk minimisation measures.

The need for a risk minimisation plan will be re-evaluated should a safety signal be detected from any source.

V.1. Routine Risk Minimisation Measures

None.

V.2. Additional Risk Minimisation Measures

None.

V.3 Summary of risk minimisation measures

None.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for *Menveo*

This is a summary of the risk management plan (RMP) for *Menveo*. The RMP details important risks of *Menveo* (if any), how these risks can be minimised, and how more information will be obtained about *Menveo*'s risks and uncertainties (missing information).

Menveo is currently available as a 2-vial or a 1-vial presentation*:*

- Powder and solution for solution for injection (*Menveo* lyo-liquid)
- Solution for injection (*Menveo* liquid)

Menveo's summary of product characteristics (SmPC) for each of the two formulations (*Menveo* lyo-liquid and *Menveo* liquid) and its package leaflet give essential information to healthcare professionals and patients on how *Menveo* should be used.

This summary of the RMP for *Menveo* should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of *Menveo*'s RMP.

I. The medicine and what it is used for

Menveo is authorised for active immunisation of children (from 2 years of age), adolescents and adults for the prevention of Invasive Meningococcal Disease (IMD) caused by *Neisseria meningitidis* groups A, C, W-135 and Y. The use of this vaccine should be in accordance with official recommendations (see SmPC for the full indication). It contains *Neisseria meningitidis* group A, C, W-135, Y oligosaccharide conjugated to *Corynebacterium diphtheriae* CRM197 protein as the active substance and it is given by intramuscular injection, preferably into the deltoid muscle.

Further information about the evaluation of *Menveo*'s benefits can be found in *Menveo*'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/menveo

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of *Menveo* (if any), together with measures to minimise such risks and the proposed studies for learning more about *Menveo*'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of *Menveo* are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of *Menveo*. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of *Menveo.*

II.C.2 Other studies in post-authorisation development plan

There are no studies required for *Menveo.*

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not Applicable.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.