NEISSERIA MENINGITIDIS GROUPS A, B, C, W, AND Y VACCINE

(PENBRAYA)

RISK MANAGEMENT PLAN

RMP version to be assessed as part of this application:

RMP Version number: 0.4

Data lock point for this RMP: 23 August 2022

Date of final sign off: 06 September 2024

Rationale for submitting an updated RMP:

The purpose of this EU RMP update version 0.4 is to include the requested changes to version 0.3, as per the CHMP and PRAC (Co-)Rapporteurs Day 195 Joint Assessment Reports received on 04 September 2024 (Procedure Number EMEA/H/C/006165/0000) and correspondence with the EMA Product Lead on 5 September 2024. Main updates include:

- Part V.1: inclusion of the Package Leaflet (Section 2 – Fertility, pregnancy, and lactation) as routine risk minimisation activity for the Missing Information "Use during pregnancy".

- Part V.3: Addition of a table summarizing the pharmacovigilance activities and the risks minimization measures for the Missing Information "Use during pregnancy".

The purpose of the EU RMP update version 0.3 was to include the requested changes to version 0.2, as per the CHMP MAA Day 180 List of Outstanding Issues received on 27 June 2024 (EMA/CHMP/291361/2024, Procedure Number EMEA/H/C/006165/0000). Main updates include:

- Inclusion of "Use during pregnancy" as Missing Information in the list of the safety concerns.

- Inclusion of the pregnancy registry study C3511007 as a PASS category 3 in the pharmacovigilance plan to address the missing information "Use during pregnancy".

- Inclusion of the follow-up questionnaire for the exposure during pregnancy in the Annex 4 of the RMP.

- Removal of the missing information "Vaccine effectiveness" from Part II, Module SVII.1, in line with the removal of this MI in the previous RMP version 0.2, as requested by the Assessor.

- Inclusion of the routine risk minimisation measures to address the missing information “Use in pregnancy” in Part V.

- Update of Part VI “Summary of activities in the risk management plan by medical product”, in line with the issues raised in other parts of the RMP.

Summary of significant changes in this RMP:

RMP Part/Module	Major Change(s)
PART I. PRODUCT OVERVIEW	Changes to common name, "Dosage in the EEA" and "Pharmaceutical form(s) and strengths", in line with the updated SmPC.
PART II SAFETY SPECIFICATION	See updates in each module.
Module SI. Epidemiology of the Indications and Target Population	No updates.
Module SII Non-Clinical Part of the Safety Specification	No updates.
Module SIII. Clinical Trial Exposure	No updates.
Module SIV. Populations Not Studied in Clinical Trials	Updated in Part II, Module SIV.1, Table 8 to reflect the inclusion of "Use during pregnancy" as missing information.
Module SV. Post-Authorisation Experience	No updates.
Module SVI. Additional EU Requirements for the Safety Specification	No updates.
Module SVII. Identified and Potential Risks	"Vaccine effectiveness" removed as missing information from Part II, Module SVII.1.
Module SVIII. Summary of the Safety Concerns	Addition of "Use during pregnancy" as missing information.
PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)	Pregnancy registry study C3511007 added in the list of additional pharmacovigilance activities as a PASS category 3 to address the added missing information in Part III.2. "Use during pregnancy". Exposure During Pregnancy F/UP Questionnaire included in Part III.1.
PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES	No updates.
PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	Routine risks minimization for "Use during pregnancy" added. Part V.1: inclusion of the Package Leaflet (Section 2 – Fertility, pregnancy, and lactation) as routine risk minimisation activity for the Missing Information "Use during pregnancy". Part V.3: Addition of a table summarizing the pharmacovigilance activities and the risks minimization measures for the Missing Information "Use during pregnancy".
PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN	Part VI updated according to the changes in the RMP from Part I to Part V, to incorporate the requested changes in Part V.

RMP Part/Module	Major Change(s)
PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN	Annex 2: updated based on the PART III of this RMP (Pregnancy registry study C3511007 added as a PASS category 3 to address the MI "Use during pregnancy". Annex 3: Study C3511007 added. Annex 4: updated to include the follow-up questionnaire for the exposure during pregnancy. Annex 8: updated to reflect the update of Part V to add the package Leaflet (Section 2) as rRMM for the Missing Information "Use during pregnancy". No updates to the other Annexes.

Other RMP versions under evaluation: None

QPPV name[1]: Barbara De Bernardi

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

LIST OF ABBREVIATIONS

4CMenB	recombinant meningococcal serogroup B vaccine
ADR	Adverse Drug Reaction
AE	adverse event
ATC	Anatomical Therapeutic Chemical
CDC	Center for Disease Control and Prevention
CFR	case fatality rate
CHMP	Committee for Medicinal Products for Human Use
CT	clinical trial
DLP	Data-Lock Point
ECDC	European Centre for Disease Prevention and Control
EDP	exposure during pregnancy
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
F/UP	Follow-up
hSBA	serum bactericidal assay with exogenous human complement
HIV	human immunodeficiency virus
HMA	Heads of Medicines Agencies
IM	intramuscular
IMD	invasive meningococcal disease
INN	International Non-proprietary Name
IV	intravenous
LMP	last menstrual period
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MenABCWY	Meningococcal groups A, C, W, Y conjugate and group B vaccine (recombinant, adsorbed)
MCM	major congenital malformation
MenB	*Neisseria meningitidis* group B
MenACWY-CRM	Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (Menveo)
MenACWY-TT	meningococcal polysaccharide groups A, C, W-135, and Y tetanus toxoid conjugate vaccine (Nimenrix®)
MenB-fHbp	meningococcal group B factor H binding protein
MCM	major congenital malformation
MI	Missing information
NA	not applicable
PAES	Post-Authorisation Efficacy Study Post-Authorisation Safety Study
PASS	Post-Authorisation Safety Study
PL	Package Leaflet
PSUR	periodic safety update report
PT	Preferred Term
PV	pharmacovigilance
RMP	Risk management plan
SAB	Spontaneous abortion
SGA	Small for gestational age
SmPC	Summary of Product Characteristics
TESSy	The European Surveillance System
UK	United Kingdom
US	United States
WHO	World Health Organization

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PART I. PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	*Neisseria meningitidis* groups A, C, W, and Y polysaccharides, conjugated to tetanus toxoid (TT) carrier protein, and *Neisseria meningitidis* group B fHbp subfamily A and B adsorbed on aluminium phosphate [Meningococcal groups A, C, W, Y conjugate and group B vaccine (recombinant, adsorbed)].
Pharmacotherapeutic group(s) (ATC Code)	Vaccines, meningococcal vaccines (J07AH11).
Marketing Authorisation Applicant	Pfizer Europe MA EEIG.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Penbraya.
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class: Meningococcal vaccine. Penbraya is a powder and suspension for intramuscular injection.
	Summary of mode of action: Penbraya induces the production of bactericidal antibodies specific to the capsular polysaccharides of *N meningitidis* groups A, C, W, and Y and to the fHbp subfamily A and B variants of *N meningitidis* group B. Anti-meningococcal antibodies protect against IMD via complement mediated bactericidal activity.
	Important information about its composition: Each 0.5 mL dose of Penbraya contains 5 mcg of each *N meningitidis* groups A, C, W, and Y, 60 mcg of each *N meningitidis* group B fHbp subfamily A and B, 44 mcg of TT carrier protein, 0.25 mg of aluminium phosphate. Powder excipients: Sucrose, Trometamol, Sodium hydroxide (for pH adjustment), Hydrochloric acid (for pH adjustment). Suspension excipients: Histidine, Polysorbate 80, Sodium chloride, Water for injections, Sodium hydroxide (for pH adjustment), Hydrochloric acid (for pH adjustment).
Hyperlink to the Product Information:	Please refer to Module 1.3.1 of this submission.
Indication in the EEA	Proposed: Penbraya is indicated for active immunisation of individuals 10 years and older to prevent invasive disease caused by *Neisseria meningitidis* groups A, B, C, W, and Y.
Dosage in the EEA	Proposed: *Primary vaccination* Two (2) doses should be administered (0.5 ml each) 6 to 12 months apart for prevention of meningococcal disease caused by groups A, B, C, W, and Y. *Booster* A booster dose should be considered for individuals at continued risk of invasive meningococcal disease who completed primary vaccination with Penbraya or completed primary vaccination with Trumenba and a meningococcal serogroups A, C, W, and Y vaccine.

Pharmaceutical form(s) and strengths	Proposed: Powder and suspension for suspension for injection. The powder is white. The liquid suspension is white.
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population(s)

Indication: Active immunization to prevent invasive disease caused by *N meningitidis* groups A, B, C, W, and Y in individual 10 years and older.

The World Health Organization (WHO) has identified twelve serogroups of *N meningitidis* based on immunologic differences in their polysaccharide capsule. Six of these serogroups (A, B, C, W, X and Y) are responsible for the vast majority of invasive meningococcal disease (IMD)[1,2], which most commonly presents as meningitis, septicemia, or a combination of both.[2,3]

The European Centre for Disease Prevention and Control (ECDC) publishes annual reports on infectious diseases, including meningococcal disease. For the most recent surveillance report on meningococcal disease, published in 2022 based on 2018 reporting, 30 European Union (EU)/ European Economic Area (EEA) countries provided case information, including the United Kingdom (UK)[4]. Of these 30 countries, 25 have a compulsory and comprehensive surveillance system; 1 has a comprehensive surveillance system (UK); 4 have a voluntary system (Belgium, Italy, Spain and the Netherlands) and of these voluntary systems 2 are sentinel based (Belgium and Spain)[5]. The majority of countries have a passive surveillance system but 3 countries characterize their systems as active (Belgium, the Czech Republic and Slovakia)[5]. Only laboratory-confirmed cases of meningococcal disease are considered for presentation. For this review, European estimates of incidence were derived from the ECDC system unless otherwise noted.

In the United States (US), meningococcal disease is a reportable condition to local and state health departments. The Centers for Disease Control and Prevention (CDC) monitors nationwide meningococcal data using both the national notification system as well as laboratory surveillance. As of 2015, the CDC has employed additional enhanced surveillance techniques to ensure a more complete picture of the epidemiology of meningococcal disease in the US.[6]

Summary of Literature Search Methods

A literature review was conducted to evaluate the epidemiology of meningococcal disease in Europe (EU/EEA, including UK) and the US. PubMed was searched to identify published articles that contained potentially relevant information on the epidemiology of meningococcal disease from January 2017 through August 2022. Keywords related to incidence, prevalence, and epidemiology were combined with terms representing meningococcal disease. The initial search focused on systematic literature reviews and meta-analyses. Important citations referenced within reviewed articles were obtained if relevant.

In addition, health statistics published by the ECDC and CDC were obtained to provide contemporary data on meningococcal epidemiology in Europe and the US.

Incidence:

In 2018, there were 3,233 confirmed cases of meningococcal disease reported across the European Union (EU)/European Economic Area (EEA), which included 30 reporting Member States. The overall reporting rate of 0.6 per 100,000 persons was similar to the reporting rate in the 2015-2017 period.[4] However, there was variability across countries, from a low incidence of 0 cases in Iceland to an incidence of 1.8 per 100,000 persons reported in Ireland.[4]

In 2019, in the US, there were 375 reported cases of meningococcal disease, for an overall incidence of 0.11 per 100,000.[7] In the US, incidence of meningococcal disease began to decline in 1995 and has remained low over the past few years, through 2019.[6]

Prevalence:

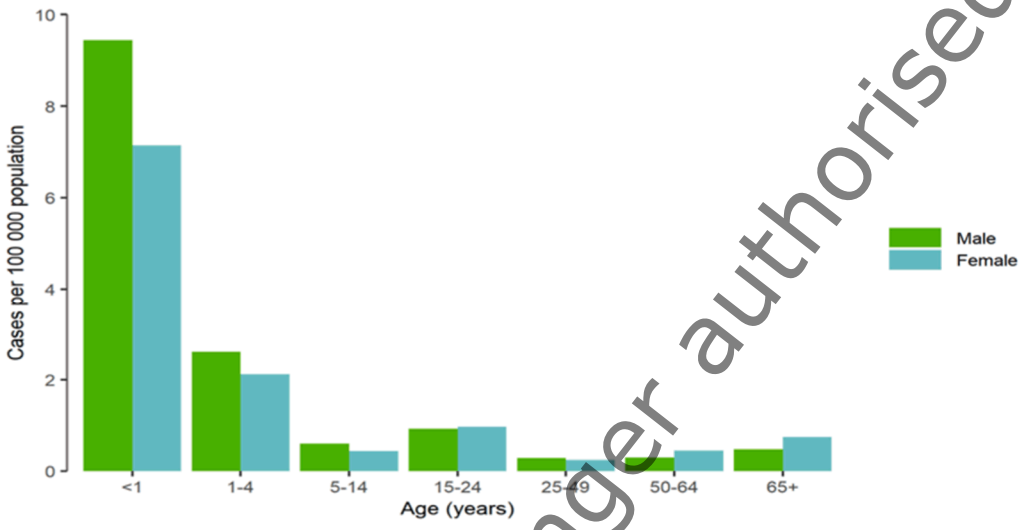
Meningococcal disease is an acute infectious disease. Because of the short (acute) duration of disease, incidence is equivalent to prevalence; and as a result, there are no epidemiologic studies reporting the prevalence of meningococcal disease.

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Age and serogroup distribution

The incidence of meningococcal disease varies greatly across age strata, with the highest rates typically reported in children aged 4 years and younger. In 2018, the reporting rate of meningococcal disease in the EU/EEA was 8.3 per 100,000 children under 1 year of age and 2.4 in children aged 1 to 4 years.[4] All other age groups had lower reporting rates; however, there was a notable second peak among those aged 15-24 years of age (0.9 per 100,000 persons), as demonstrated in Figure 1.[4] Data show similar trends for incidence by age in the US, with the highest incidence in 2019 in those age 4 years or younger, a notable peak in those aged 16 to 23 years of age, and a slightly elevated incidence among those age 65 years or older.[7]

Figure 1. Incidence of Meningococcal disease in EU/EEA 2018, by age and sex

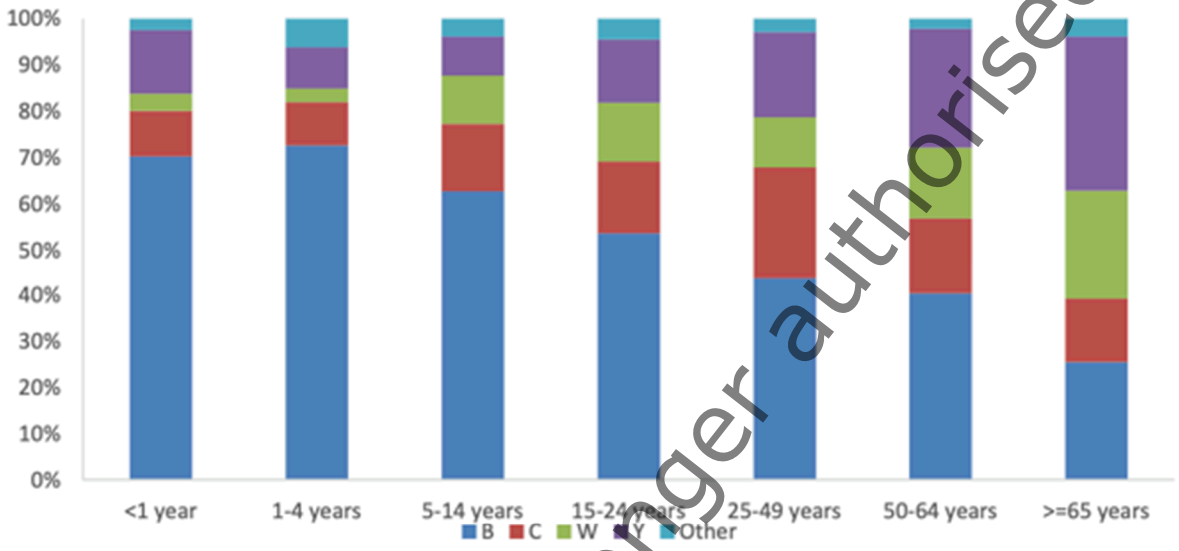


Source: Country reports from Austria, Belgium, Bulgaria, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom.

SOURCE: Figure in the ECDC Invasive Meningococcal Disease Annual Epidemiological Report for 2018, based on data from The European Surveillance System (TESSy).[4]

Overall, serogroup B accounted for 51% of cases of meningococcal disease in the EU/EEA in 2018, followed by W (18%), C (15%), Y (12%) and other (4%; other consists of "A, X, Z, 29E, non-groupable or 'other'). Importantly, as shown in Figure 2, the distribution of serogroup varied with age.[4] Whereas serogroup B accounted for over half of the cases among children and young adults (and over two-thirds of cases among those through age 4), serogroups W and Y accounted for 58% of the cases among those aged 65 years or older.[4]

Figure 2. Serogroup distribution, by age, among cases of meningococcal disease in EU/EEA in 2018



'Other' refers to all cases reported as serogroup A, X, Z, 29E, non-groupable or 'other'.

Source: Country reports from Austria, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom.

Among 25 Member States that consistently reported serogroup data from 2014 to 2018, the overall notification rates of serogroup B fluctuated between 0.30–0.34 per 100 000 during the last five years (Figure 6). There was a decrease observed in children <1 year of age from 7.8 to 6.0 per 100 000. It fluctuated between 1.7 and 2.1 very per 100 000 in 1-4-year-olds, between 2014 and 2017.

The incidence of serogroup W continuously increased (from 0.04 to 0.12 per 100 000) between 2014 and 2018. The increase was observed in all age groups (Figure 7) but was more pronounced in extreme age groups. The incidence per 100 000 in 2014 and 2018 were 1.2 and 1.6 in children <1 year, 0.11 and 0.24 in children 1–4 years, 0.03 and 0.10 in adults 50–64 years and 0.1 and 0.25 in adults 65 years or above respectively.

The notification rates of serogroups C and Y have fluctuated between 0.08–0.10 and 0.05–0.07 per 100 000 respectively during the last 5 years. An increased trend was observed for serogroup Y.

Source:Figure in the ECDC Invasive Meningococcal Disease Annual Epidemiological Report for 2018, based on data from The European Surveillance System (TESSy)[4].

Further, while the incidence of most serogroups remained relatively stable between 2014 and 2018, the incidence of serogroup W increased throughout the period, from 0.04 per 100,000 persons in 2014 to 0.12 per 100,000 persons in 2018. This increase was seen among patients of all ages but was greatest among the youngest children (those through age 4 years) and adults aged 50 years or older.[4]

A recent analysis of European data found that, while overall incidence of meningococcal disease decreased 34.4% over the 10-year period 2008-2017 from 0.95 per 100,000 persons in 2008 to 0.62 per 100,000 persons in 2017, there were marked age-related differences in these changes.[8] Whereas the youngest age groups experienced sharp decreases in incidence (54.1% decrease among infants and 55.7% decrease among 1-4 year old children), adults aged 65 years or older actually experienced a 51.7% increase in incidence over that time.[8] Further, among adolescents and young adults, although they

experienced some decrease in meningococcal disease due to serogroup B, these age groups experienced an increase in infections attributable to serogroups W and Y.[8]

Serogroup distribution differed in the US compared to the overall distribution in the EU/EEA, with 26% of cases attributable to B, 23% of cases attributable to C, 18% attributable to Y, 11% attributable to W and the remainder considered nongroupable or other/unknown.[7] However, similar to what was observed in the EU/EEA, in the US serogroup B was predominant among children (accounting for 46% of cases in those through age 4 years) as is shown in Table 1.[7]

Table 1. Meningococcal disease cases by age and serogroup in the US in 2019

Age (years)	**B** No. (Incidence[a])	**C** No. (Incidence[a])	**W** No. (Incidence[a])	**Y** No. (Incidence[a])	**Nongroupable** No. (Incidence[a])	**Other[b]/Unknown** No. (Incidence[a])	**Total** No. (Incidence[a])
<1	16 (0.42)	4 (0.11)	0 (0.00)	4 (0.11)	3 (0.08)	4 (0.11)	31 (0.82)
1-4	12 (0.08)	10 (0.06)	2 (0.01)	1 (0.01)	1 (0.01)	4 (0.03)	30 (0.19)
5-10	0 (0.00)	5 (0.02)	0 (0.00)	1 (0.00)	0 (0.00)	1 (0.00)	7 (0.03)
11-15	2 (0.01)	4 (0.02)	0 (0.00)	0 (0.00)	1 (0.00)	2 (0.01)	9 (0.04)
16-23	21 (0.06)	1 (0.00)	1 (0.00)	3 (0.01)	11 (0.03)	6 (0.02)	43 (0.13)
24-44	21 (0.02)	13 (0.01)	8 (0.01)	19 (0.02)	9 (0.01)	10 (0.01)	80 (0.09)
45-64	12 (0.01)	28 (0.03)	11 (0.01)	20 (0.02)	5 (0.01)	11 (0.01)	87 (0.10)
65	15 (0.03)	20 (0.04)	18 (0.03)	20 (0.04)	7 (0.01)	8 (0.01)	88 (0.16)
Total	**99 (0.03)**	**85 (0.03)**	**40 (0.01)**	**68 (0.02)**	**37** (0.01)	**46 (0.01)**	**375 (0.11)**

Includes all confirmed and probable cases reported from all jurisdictions.
a. Cases per 100,000 population.
b. Includes 3 serogroup E cases.
SOURCE: CDC - National Center for Immunization and Respiratory Diseases; Office of Infectious Diseases[7]

Gender

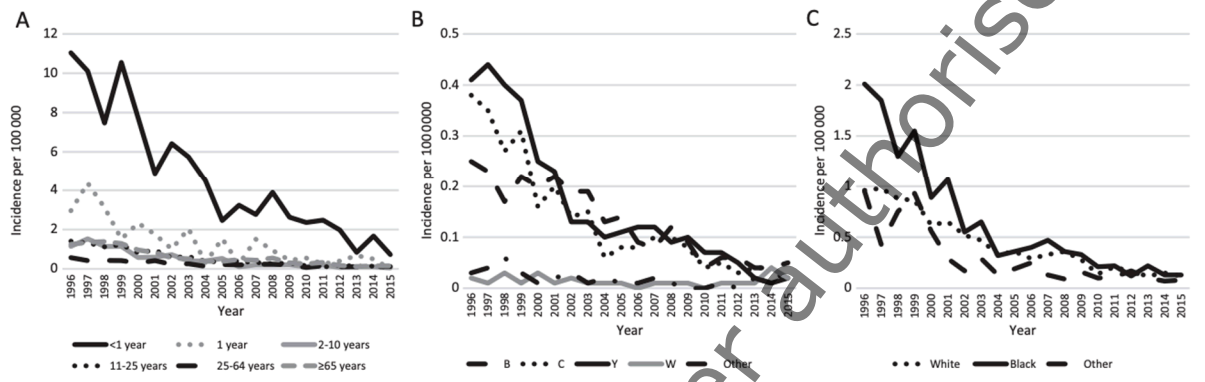
Overall, rates of meningococcal disease were similar between males and females in the EU/EEA; however, age-specific variation existed. Whereas meningococcal disease was slightly more common among male children than in female children, among adults aged 50 years or older the reverse was observed, with rates slightly higher in females, as is demonstrated in Figure 1, from the ECDC report.[4]

Data on gender distribution were not reported in the US CDC report. However, a recent meta-analysis, which included data at the national level from 10 countries (including 6 in Europe), found similar results to that in the ECDC report, with the incidence of meningococcal disease higher in young males compared to young females, but among older persons the incidence was higher in females compared to males.[9]

Race/Ethnicity

Information on meningococcal disease by race were not identified for Europe. In the US, incidence observed during 2006-2015 was 0.27 per 100,000 among Black persons, incidence among White persons was 0.20 per 100,000 persons, 0.20 per 100,000 among persons of other races. However, these differences lessened over time, as is demonstrated in the third panel of Figure 3.[10]

Figure 3. Incidence of meningococcal disease in the US (1996-2015) by age (A), serogroup (B), and race (C)



SOURCE: Figure in Current Epidemiology and Trends in Meningococcal Disease–United States, 1996–2015, based on data from the CDC Active Bacterial Core surveillance system.[10]

Carriage

Nasopharyngeal colonization by *N meningitidis* is relatively common and is generally asymptomatic. However, for unclear reasons, only a small percentage of colonized persons develop disease. Prevalence of meningococcal carriage can vary across age groups and settings.[11,12,13] A systematic review found that age was the most important predictor of carriage, with carriage being fairly low among children (estimated at 4.5% in infants and 7.7% in children 10 years of age) and increasing with age to peak at 19 years of age (estimated at 23.7%), followed by a subsequent decrease in carriage prevalence (7.8% among adults 50 years of age).[11]

In a more recent systematic review and meta-analysis of publications of carriage rates for specific serogroups published from 2007-2016, the vast majority of studies focused on teenagers and young adults.[13] In European studies, serogroup B was the most commonly found of the disease-associated serogroups, with a carriage prevalence of 1.9% among persons aged 11-17 years of age and 5% among persons aged 18-24 years.[13] In the Americas region, serogroups B and C represented the most prevalent of the disease-associated serogroups among persons aged 18-24 years, with respective carriage prevalences of 1.6% and 2.5%.[13]

Once an individual has become colonized with *N meningitidis*, the likelihood of acquiring invasive meningococcal disease depends on the virulence of the particular organism, host factors affecting innate susceptibility, and the presence or absence of serum antibodies capable of activating complement-mediated bacteriolysis and clearing of the organism from the blood stream.[14,15]

Outbreaks

Despite advances in public health measures and vaccination, outbreaks of meningococcal disease continue to occur. Similarly, some areas experience periods of ongoing elevated incidence of meningococcal disease.[16] Of importance, studies suggest that within an outbreak setting the case fatality rate (CFR) is higher than that due to endemic disease alone.[17] In 2018, 4.2% of meningococcal disease cases in the US were found to be outbreak related.[7]

As of October 2022, there is a potential ongoing outbreak of meningococcal disease in Ireland, with 3 confirmed and 1 probable case reported through September 2022, two of which were fatal. There is no known epidemiologic link across the cases and this situation is currently being monitored.[18] As of October 2022, there is an ongoing outbreak of serogroup C meningococcal disease in the US, primarily among gay and bisexual men in Florida.[19] A June 2022 report stated that, at that time, there had been at least 24 cases reported and at least 6 deaths attributable to this outbreak in Florida.[20]

Examples of recent outbreaks in Europe include a meningococcal B outbreak at a Belgian nursery school (3 cases, 0 deaths, 2018);[21] a meningococcal B outbreak in a small community in France (4 cases, 0 deaths, 2016);[22] a meningococcal B outbreak in an Italian community (7 cases, 2 deaths, 2018);[23] and a meningococcal C outbreak in another Italian community, primarily among bisexuals and men who have sex with men (62 cases, 13 deaths, 2015-2016).[24]

Students living on college campuses in the US are at increased risk for experiencing a meningococcal outbreak. In a review of meningococcal cases in the US which occurred from 2014-2016, there were 6 identified outbreaks among college campuses, all caused by serogroup B, accounting for 30% of all serogroup B cases among 18 to 24 year-old during this period.[25] In addition to these cases among college students, among other 18-24 year-old persons in the US not attending college during this time there were 3 outbreaks of serogroup C meningococcal disease among men who have sex with men and 1 outbreak of serogroup C/Y among persons experiencing homelessness.[25]

Vaccination

Significant variation in vaccination recommendations exists across countries[26,27] with country specific recommendations changing with time. This section presents the current recommendations in the EU/EEA, UK and US, as of October 2022.

As of 2022, 10 countries in the EU/EEA (Austria, the Czech Republic, France, Greece, Ireland, Italy, Lithuania, Luxembourg, Malta, and Portugal) recommend vaccination for serogroup B, on differing schedules.[27] Further, 18 EU/EEA countries (Austria, Belgium, Cyprus, Czech Republic, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Liechtenstein, Luxemburg, Malta, Netherlands, Poland, Portugal, Spain) now include routine meningococcal group C conjugate vaccination and 9 EU/EEA countries (Austria, Belgium, Czech Republic, Greece, Ireland, Italy, Malta, Netherlands, and Spain) now include routine meningococcal group ACWY conjugate vaccination. The ECDC Vaccine

Scheduler provides additional details on vaccine schedules for all EU/EEA countries as of 2022.[27]

In the UK, as of October 2022, it is recommended that meningococcal B vaccine is given at ages 8 weeks, 16 weeks and 1 year; the recommendation for the ACWY meningococcal conjugate vaccine is at 14 years of age.[28]

In the US, the most recent CDC recommendations were published in 2020.[29] The meningococcal B vaccine is recommended for persons aged 16–23 years, as well as those persons aged 10 years or older at increased risk for meningococcal disease.[29] For the ACWY conjugate vaccine, CDC recommends a first dose for all children aged 11 or 12 years and a booster at 16 years, as well as those persons aged ≥2 months at increased risk for meningococcal disease.[29]

Risk Factors

As noted above, infants and young children tend to have the highest risk for meningococcal disease; a second peak in incidence is also seen in teenagers and young adults as well as the elderly, with non-elderly adults typically showing the lowest incidence of meningococcal disease.[1,4,7,30] Additional risk factors include living on a college campus in a group setting,[25,31] homelessness,[32] travel to areas of high risk such as Africa (the "meningitis belt"), and certain medical conditions, including complement deficiency, asplenia and human immunodeficiency virus (HIV).[1,29,30] In addition to complement deficiency being a risk factor for meningococcal disease, persons who receive complement inhibitors for the treatment of other disease face an increased risk of meningococcal disease.[29,33,34] Finally, certain occupations, (eg, military recruits, microbiologists working in a laboratory with meningococcal isolates), may put persons at increased risk for meningococcal disease.[29]

A recent case-control study found that certain groups were at increased risk for meningococcal disease, including renal disease, immunological disorders, liver disease, cancer, hemolytic anemia, diabetes, neurological disease, autoimmune disease, and solid organ transplant. Further, having at least one comorbidity was associated with an increased risk of meningococcal disease.[35] Another study, which looked for risk factors for hospitalization with meningococcal disease, found that immunodeficiency (congenital or acquired) and asplenia/hyposplenia showed the greatest association with hospitalization for meningococcal disease. Other factors shown to be associated with meningococcal disease were autoimmune disorders, hemophilia, and severe chronic respiratory issues.[36]

Men who have sex with men are also considered to be at higher risk for meningococcal disease.[29] Several outbreaks of meningococcal disease have been found in clusters of men who have sex with men, including the currently ongoing (as of October 2022) outbreak of serogroup C in Florida as well as a relatively recent outbreak of Serogroup C in Tuscany, Italy.[19,20,24]

A systematic literature review looked at risk factors for meningococcal disease and found that, among the potential risk factors which were able to be included in a meta-analysis,

significant risk factors included HIV infection, passive home smoke exposure, and living in a crowded space.[37]

The main existing treatment options:

Treatment for IMD includes the tertiary prevention strategy of early antibiotic therapy to which the *N meningitidis* bacteria are susceptible. Because the course of IMD is often very rapid, delays in disease recognition often occur, and delayed initiation of antibiotics often fails to halt progression of disease, there is a high degree of morbidity and mortality despite therapy. Secondary prevention strategies through screening for infection are not feasible due to the rarity of disease and asymptomatic carriage. Therefore, primary prevention of IMD is a more effective strategy. Chemoprophylaxis, while highly effective for prevention of IMD among close contacts of diagnosed individuals, is not a sufficient or practical public health measure to prevent IMD in the general healthy EU population or during large outbreaks. Preventive vaccines provide for the possibility of the broadest protection of at risk populations and are therefore a necessary and most effective strategy for minimizing the debilitating morbidity and mortality of IMD. In Europe, there are currently licensed meningococcal conjugate vaccines for the prevention of IMD which including monovalent serogroup C and quadrivalent A, C, W, Y serogroup-containing vaccines. There are also two currently licensed vaccines in Europe for the prevention of IMD caused by serogroup B, 4CMenB and MenB-fHbp. A pentavalent A, B, C, W, and Y serogroup-containing vaccine would provide a single vaccine for the prevention of the vast majority of IMD cases in Europe.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Clinical presentation and diagnosis

Humans are the only known host for the meningococcal bacterium.[38] Some persons will experience asymptomatic nasopharynx colonization and may never progress, whereas others will progress to meningococcal disease.[38] There is a broad spectrum of clinical presentation for meningococcal infection, ranging from a mild febrile illness to the most severe meningitis and/or septicemia.[39] The early symptoms of meningitis are not necessarily specific and may share features common with other illnesses.[38]

In children and adolescents, important early signs of meningococcal infection include leg pain, cold hands and feet, and abnormal skin color which typically present in the first 12 hours of infection; the more “classic” signs of meningococcal infection, including rash, meningism (i.e., nuchal rigidity, photophobia and headache) and impaired consciousness typically occur after that first 12 hours of infection.[40]

Diagnosis is typically made from either isolation of the bacterium or detection of specific nucleic acids from a normally sterile body site.[29] It is important for clinicians to be aware of the potential signs of meningococcal disease in order to treat individual patients as soon as possible to stop what might rapidly become a serious illness, and to

hopefully stop further spread of the bacterium, even treating presumptively before laboratory confirmation.[29]

In the EU/EEA in 2018, clinical presentation data were available for 51% of the reported meningococcal disease cases. Among those with available presentation data, the breakdown was as follows: meningitis and septicemia (53%), septicemia only (37%), pneumonia only (1%) and other (9%).[4]

Mortality

In 2018, there were 324 confirmed deaths due to meningococcal disease in the EU/EEA, for an overall CFR of 12% (among the 84% of cases with a known outcome).[4] Further, CFR varied by serogroup as follows: W (19%), C (16%), Y (8%) and B (8%). Finally, CFR was highest among the oldest patients (18% among those aged 65) and 15% among those age 50-64 years old).

In the US, there were 35 confirmed deaths due to meningococcal disease in 2019, resulting in an overall CFR of 9.6% among those with a known outcome.[7] CFR varied by serogroup: Y (11.8%), C (9.6%), W (7.7%) and B (6.1%).[7] The highest CFR in the US was seen in children aged 5-10 years (16.7%, n=1), followed by adults aged 45-64 years (14.1%, n=12) and infants younger than 1 year of age (12.9%, n=4).[7]

A recent meta-analysis found evidence that persons aged 25-44 years old are at higher risk of mortality (compared to children less than 5 years of age) and infection with serogroup C was associated with a higher risk of mortality than infection with serogroup B.[37] Both the EU/EEA and US reports of meningococcal surveillance for 2018 found the lowest CFR among serogroup B patients.

Important co-morbidities:

Data on the prevalence of comorbidity in patients with meningococcal disease are limited. It has been suggested that most children and young adults who develop meningococcal disease were previously healthy, in contrast to older adults.[41,42]. A recent case-control study from Denmark found that certain groups were at increased risk for meningococcal disease, including patients with autoimmune disease, renal disease, liver disease, cancer, diabetes, neurological disease and, most of all, solid organ transplant. Further, having 1 or more comorbidity was associated with an increased risk of meningococcal disease.[35]

Module SII. Non-Clinical Part of the Safety Specification

The key safety findings from nonclinical studies and their relevance to human usage are presented in Table 2.

Table 2. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Toxicity (key issues identified from acute or repeat-dose toxicity studies). In repeat-dose toxicity studies with the individual components, MenACWY-TT and MenB-fHbp, all findings were non-adverse and consistent with an immune response to vaccine administration in rabbits and/or secondary to inflammation. Injection site reaction (oedema and/or erythema) and increase in body temperature occurred after administration of MenACWY-TT or MenB-fHpb. Additionally, increases in fibrinogen, total globulins, and creatine kinase were observed following administration of bivalent MenB-fHpb.	Findings indicative of local and systemic reactogenicity were observed in CTs with adults, adolescents, and toddlers administered MenACWY-TT and MenB-fHbp.
Reproductive/developmental toxicity The individual components, MenACWY-TT and MenB-fHbp did not affect mating, female fertility, or embryo/foetal viability, growth, and/or development of F1 foetuses and pups in rats.	There are no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response.
Genotoxicity NA	
Carcinogenicity NA	
Safety pharmacology MenACWY-TT produced no findings on cardiovascular and respiratory functions in rats.	NA
Other toxicity-related information or data NA	

Module SIII. Clinical Trial Exposure

The clinical trial development program for Penbraya consists of 1 ongoing and 2 completed trials, as indicated below.

Phase 1/2 study	**Study status: completed**
	B1971057[a] (Stage 1 and Stage 2): First-in-human Phase 1/2 study evaluating the safety, tolerability, and immunogenicity of Penbraya in healthy participants ≥10 to <26 years of age.
Phase 2b study	**Study status: ongoing**
-	C3511004[b]: A Phase 2b, Randomized, Observer-Blinded Trial to Describe the Safety, Tolerability, and Immunogenicity of Penbraya Administered on 2 Different Dosing Schedules in Healthy Participants ≥11 to <15 Years of Age.
Phase 3 study	**Study status: completed**
-	C3511001[a]: A phase 3, randomized, active-controlled, observer-blinded trial to assess the safety, tolerability, and immunogenicity of Penbraya in healthy participants ≥10 to <26 years of age.

a. This study had sites in US and EU.
b. This study had sites in US.

Across all 3 clinical trials, 4311 participants received at least 1 study vaccination: 2605 participants received Penbraya and 1706 received control vaccine (MenB-fHbp +MenACWY-CRM).

Table 3. Exposure to MenABCWY by Dose (Totals)

Exposure (No. of Doses Received)	**No. of Participants Exposed to MenABCWY**	**Total No. of Vaccine Doses**
1 Dose	441	441
2 Doses	2020	4040
Booster dose	144	432
Total	2605	4913

Note: Studies B1971057 Stage 1 and Stage 2, C3511001, and C3511004 are summarized in this table.
Note: The No. of Participants Exposed to MenABCWY were only counted once in total. The Total No. of Vaccine Doses column includes participants who received at least 1 dose of MenABCWY. All participants who received at least 1 dose of MenABCWY were counted.
Note: The data cutoff dates are 03MAY2019 (B1971057 Stage 1), 03AUG2022 (B1971057 Stage 2), 23AUG2022 (C3511001), and 02JUN2022 (C3511004).
[redacted] Source Data: adsl Output File: ./nda1/C351_Integrated_RMP_2022/exp_rmp Date of Generation: 17NOV2022 (12:11)

Table 4. Exposure to MenABCWY by Age Group and Dose

Age Group Exposure (No. of Doses Received)	No. of Participants Exposed to MenABCWY	Total No. of Vaccine Doses
10 to <18		
1 Dose	325	325
2 Doses	1372	2744
Booster Dose	94	282
Total	1791	3351
18 to <26		
1 Dose	116	116
2 Doses	648	1296
Booster Dose	50	150
Total	814	1562

Note: Studies B1971057 Stage 1 and Stage 2, C3511001, and C3511004 are summarized in this table.
Note: The No. of Participants Exposed to MenABCWY were only counted once in total. The Total No. of Vaccine Doses column includes participants who received at least 1 dose of MenABCWY. All participants who received at least 1 dose of MenABCWY were counted.
Note: Age group = Participant age at time of study entry.
Note: The data cutoff dates are 03MAY2019 (B1971057 Stage 1), 03AUG2022 (B1971057 Stage 2), 23AUG2022 (C3511001), and 02JUN2022 (C3511004).
[redacted] Source Data: adsl Output File: ./nda1/C351_Integrated_RMP_2022/exp_rmp_age_dose Date of Generation: 22NOV2022 (15:30)

Table 5. Exposure to MenABCWY by Age Group and Gender

	No. of Participants Exposed to MenABCWY		Total No. Vaccine Doses	
Age Group	Male	Female	Male	Female
10 to <18	944	847	1762	1589
18 to <26	313	501	604	958
Total	1257	1348	2366	2547

Note: Studies B1971057 Stage 1 and Stage 2, C3511001, and C3511004 are summarized in this table.
Note: The No. of Participants Exposed to MenABCWY were only counted once in total. The Total No. of Vaccine Doses column includes participants who received at least 1 dose of MenABCWY. All participants who received at least 1 dose of MenABCWY were counted.
Note: Age group = Participant age at time of study entry.
Note: The data cutoff dates are 03MAY2019 (B1971057 Stage 1), 03AUG2022 (B1971057 Stage 2), 23AUG2022 (C3511001), and 02JUN2022 (C3511004).
[redacted] Source Data: adsl Output File: ./nda1/C351 Integrated RMP 2022/exp rmp age Date of Generation: 22NOV2022 (15:32)

Table 6. Exposure to MenABCWY by Racial and Ethnic Origin (Totals)

	No. of Participants Exposed to MenABCWY	Total No. of Vaccine Doses
Racial Origin		
White	2085	3980
Black or African American	261	456
Asian	53	102
American Indian or Alaskan Native	11	19
Native Hawaiian	6	9
Not Reported	133	241
Other[a]	56	106
Ethnic Origin		
Hispanic/Latino	552	986
Non-Hispanic/non-Latino	2039	3902
Not reported	13	23
Unknown	1	2
Total	2605	4913

Note: Studies B1971057 Stage 1 and Stage 2, C3511001, and C3511004 are summarized in this table.
Note: The No. of Participants Exposed to MenABCWY were only counted once in total. The Total No. of Vaccine Doses column includes participants who received at least 1 dose of MenABCWY. All participants who received at least 1 dose of MenABCWY were counted.
Note: The data cutoff dates are 03MAY2019 (B1971057 Stage 1), 03AUG2022 (B1971057 Stage 2), 23AUG2022 (C3511001), and 02JUN2022 (C3511004).
a. Racial Origin categories other than White, Black, Asian, Native Hawaiian, American Indian or Alaskan Native are combined into a separate category termed "Other".
[redacted] Source Data: adsl Output File: ./nda1/C351 Integrated RMP 2022/exp rmp race Date of Generation: 14DEC2022 (09:32)

Table 7. Exposure to MenABCWY by Age Group, Racial and Ethnic Origin

Age Group	No. of Participants Exposed to MenABCWY	Total No. of Vaccine Doses
10 to <18		
Racial Origin		
White	1375	2597
Black or African American	199	356
Asian	31	60
American Indian or Alaskan Native	9	16
Native Hawaiian	6	9
Not Reported	128	231
Other[a]	43	82
Ethnic Origin		

Table 7. Exposure to MenABCWY by Age Group, Racial and Ethnic Origin

Age Group	No. of Participants Exposed to MenABCWY	Total No. of Vaccine Doses
Hispanic/Latino	463	833
Non-Hispanic/non-Latino	1321	2505
Not reported	6	11
Unknown	1	2
Total	1791	3351
18 to <26		
Racial Origin		
White	710	1383
Black or African American	62	100
Asian	22	42
American Indian or Alaskan Native	2	3
Native Hawaiian	0	0
Not Reported	5	10
Other[a]	13	24
Ethnic Origin		
Hispanic/Latino	89	153
Non-Hispanic/non-Latino	719	1398
Not reported	7	12
Total	815	1563

Note: Studies B1971057 Stage 1 and Stage 2, C3511001, and C3511004 are summarized in this table.
Note: The No. of Participants Exposed to MenABCWY were only counted once in total. The Total No. of Vaccine Doses column includes participants who received at least 1 dose of MenABCWY. All participants who received at least 1 dose of MenABCWY were counted.
Note: The data cutoff dates are 03MAY2019 (B1971057 Stage 1), 03AUG2022 (B1971057 Stage 2), 23AUG2022 (C3511001), and 02JUN2022 (C3511004).
Note: Age group = Participant age at time of study entry.
a. Racial Origin categories other than White, Black, Asian, Native Hawaiian, American Indian or Alaskan Native are combined into a separate category termed "Other".
[redacted] Source Data: adsl Output File: ./nda1/C351 Integrated RMP 2022/exp rmp age race Date of Generation: 14DEC2022 (09:46)

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 8. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criteria	Reason for Exclusion	Missing Information (Yes/No)	Rationale (if not included as missing information)
Previous vaccination with any meningococcal group B vaccine, any purely polysaccharide (nonconjugate) meningococcal vaccine, or monovalent/bivalent meningococcal vaccine.	To avoid confounding the assessment of immune response in the study population.	No	Minimal potential impact on target population.
Previous vaccination with >1 dose of a vaccine containing 1 or more ACWY group or participants having received 1 prior dose of a vaccine containing 1 or more ACWY group <4 years prior to the date of randomization.	To avoid confounding the assessment of ACWY immune response in the study population.	No	Minimal potential impact on the target population.
A known or suspected defect of the immune system that would prevent an immune response to the vaccine, such as participants with congenital or acquired defects in B-cell function, those receiving chronic systemic (oral, IV, or IM) corticosteroid therapy, or those receiving immunosuppressive therapy.	To avoid confounding the assessment of immune response in the study population.	No	It is not expected that use of the vaccine in such patients would be associated with a different safety profile. Information concerning the possibility to have a reduced immune response in this population is provided in the SmPC Section 4.4 *Special warnings and precautions for use.*
History of microbiologically proven disease caused by *N meningitidis* or *N. gonorrhoeae*.	To avoid confounding the assessment of immune response in the study population.	No	No impact on the safety of the target population.
Current chronic use of systemic antibiotics.	Presence of antibiotics in the participants' serum may interfere with the growth of *N meningitidis* in the hSBA assay, thereby invalidating interpretation of the assay.	No	No impact on the safety of the target population.

Table 8. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criteria	Reason for Exclusion	Missing Information (Yes/No)	Rationale (if not included as missing information)
Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behaviour, recent (within the past year) hospitalization for psychiatric illness, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgement of the investigator, would make the participant inappropriate for entry into this study.	To increase likelihood that enrolled participants continue study participation by limiting to healthy individuals without underlying conditions that could interfere with interpretation of study results, reduce compliance, or increase risk of not completing study.	No	No impact on the safety of the target population.
Significant neurological disorder or history of seizure (excluding simple febrile seizure).	To minimize confounding of assessing relatedness of emergent neurological disorder or worsening of existing conditions.	No	No impact on the safety of the target population.
Any neuro-inflammatory or autoimmune condition, including, but not limited to, transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.	To minimize confounding of assessing relatedness of emergent autoimmune and neuroinflammatory conditions or worsening of existing conditions.	No	No impact on the safety of the target population.
A previous anaphylactic reaction to any vaccine or vaccine-related component.	To ensure the safety of the study population.	No	Information concerning this criterion is provided in the SmPC Section 4.3 *Contraindications*.
Pregnant women.	To ensure the safety of the study population.	Yes	Not applicable.
Breastfeeding women.	To ensure the safety of the study population.	No	Based on the clinical and post-marketing safety experience of MenB-fHbp and MenACWY-TT, no different safety profile during lactation is anticipated for Penbraya. Information regarding use during lactation is provided in the SmPC Section 4.6 *Fertility, pregnancy and lactation*.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The limitations from clinical trials to detect rare AEs are compensated by the extensive MenB-fHbp (>8 years) and MenACWY-TT (>10 years) post-marketing exposure.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 9. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program. As of the DLP of this RMP, 36 reports of pregnancy had been received from clinical trials, of which 18 occurred in the Penbraya group [B1971057 (11); C3511001 (7)] and 18 in the Control group (Trumenba+MenACWY-CRM); none reported associated clinical adverse events (AEs). In the Penbraya group (18 cases) • The following PTs were reported: o Maternal exposure before pregnancy (8 cases); o Maternal exposure during pregnancy (10 cases). • Pregnancy occurred in participants who received the last vaccination: o more than 30 days prior to the estimated date of conception (distal pregnancies, 16 cases), o within 30 days prior to the estimated date of conception (proximate pregnancy, 1 case). o In 1 case it was unknown if it was a distal or a proximate pregnancy. • Pregnancy outcomes was known in 11 cases out of 18: o Live births (7) ✓ Full term, Normal (6) ✓ Premature, perinatal complication (1) o Fetal loss (4) ✓ Spontaneous abortion (3) ✓ No data (1) • In 7 cases, participants were lost to follow-up.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular disease • Immunocompromised patients	Not included in the clinical development program.
Population with relevant different racial and ethnic origin.	Please refer to Module SIII, Table 6 and Table 7 for exposure information by racial origin from the studies.

Table 9. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Subpopulations carrying relevant genetic polymorphisms	No host genetic polymorphism has been identified that would have a substantial influence on the immune response to Penbraya vaccine.
Other	N/A

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

No market exposure information is currently available.

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

Penbraya does not have characteristics that would make it attractive for use for illegal purposes. No potential for drug abuse or dependence with Penbraya is expected.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Table 10 lists the safety concerns in the initial RMP submission for Penbraya.

Table 10. Safety Concerns at the Initial RMP Submission

Safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use during pregnancy

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not all potential or identified risks for the vaccine are considered to meet the level of importance necessitating inclusion in the list of safety concerns in the RMP.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

A review of the safety data from the completed Phase 3 study C3511001[2], from the completed Phase 1/2 study B1971057 and from the ongoing Phase 2b study C3511004 of Penbraya in adolescents and adults did not identify any risks beyond those already known for

[2] This study ongoing at the cut-off date of 23 August 2022, was completed (concluded with a final clinical study report) after the data-lock point.

the vaccine's individual components (MenB-fHbp and MenACWY). Known risks that require no further characterisation and are followed up via routing pharmacovigilance namely through signal detection and adverse reaction reporting includes Local and systemic reactogenicity events.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risks: None

Important Potential Risks: None.

Missing information: Use during pregnancy.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable; this is an initial RMP submission for Penbraya.

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

As stated above, there are no important identified or potential risks for Penbraya.

SVII.3.2. Presentation of the Missing Information

Use during pregnancy:

Evidence source:

Pregnant women were not eligible for participation in the pivotal studies. However, based on the clinical and post-marketing safety experience of MenB-fHbp and MenACWY-TT, no different safety profile in pregnant women is anticipated for Penbraya. "Use during pregnancy" is added as missing information as requested by the CHMP.

Population in need of further characterisation:

- Individuals vaccinated during pregnancy.

The lack of data is communicated in product labeling; for the non-interventional study of the safety and immunogenicity on MenABCWY in pregnant women, see Section III.2 and Section III.3.

Module SVIII. Summary of the Safety Concerns

Table 11. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use during pregnancy

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

- Specific adverse reaction follow-up questionnaires for safety concern

Routine pharmacovigilance activity is conducted for spontaneous reports of exposure during pregnancy, aligned with the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP), Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data (May 2006). Pfizer pursues follow-up information in all reported cases of exposure during pregnancy using an Exposure During Pregnancy (EDP) Follow-Up Questionnaire (Annex 4). The range of information requested includes demographic information, current and past pregnancy and obstetrical information, details on drug use by the pregnant female (including the Pfizer product, non-Pfizer products, and illicit drugs), and delivery details. Information is also requested about the neonate, including measurements after birth, the presence of congenital or developmental abnormalities, illnesses, hospitalisation, and breastfeeding information. Relevant paternal health and exposure information is also queried.

- Other forms of routine pharmacovigilance activities for safety concerns

If Penbraya is used as part of a national immunisation programme or in a large outbreak situation, the MAH will review and summarize, in the PSUR, national surveillance data for IMD (serogroups A, B, C, W, Y), as available.

III.2. Additional Pharmacovigilance Activities

There is one category 3 registry PASS study for Penbraya.

Study C3511007: A pregnancy registry study to evaluate the safety of PENBRAYA™ meningococcal vaccine exposure during pregnancy.

Rationale and study objective: To estimate the proportion of major congenital malformation (MCM), spontaneous abortion (SAB), elective termination, stillbirth, preterm birth, and small for gestational age (SGA) among individuals exposed to PENBRAYA during pregnancy or within 30 days prior to last menstrual period (LMP).

Study design: This registry-based, prospective, observational cohort study will enroll and follow pregnant individuals 10 through 25 years of age in the US who are exposed to PENBRAYA during pregnancy.

Study population: All participants will be followed through the end of pregnancy, and all liveborn infants will be followed through 12 months of age. The total study duration will be approximately 8 years to allow for sufficient follow-up time for the last enrolled participant and liveborn infant.

Planned Milestones:

- ✓ Final study report: 30 April 2033

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

As stated in Part III.2, there is 1 category 3 registry PASS study for Penbraya.

Table 12. Additional Pharmacovigilance Activities

Protocol no/ *Status*.	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones	Dates
C3511007 *Planned*	A pregnancy registry study to evaluate the safety of PENBRAYA™ meningococcal vaccine exposure during pregnancy.	To estimate the proportion of MCM, SAB, elective termination, stillbirth, preterm birth, and SGA among individuals exposed to PENBRAYA during pregnancy or within 30 days prior to LMP.	This registry-based, prospective, observational cohort study will enrol and follow pregnant individuals 10 through 25 years of age in the US who are exposed to Penbraya during pregnancy. Participation in the registry is voluntary and participants can withdraw their consent to participate any time.	Pregnant individuals 10 through 25 years of age in the US who are exposed to PENBRAYA during pregnancy.	Final study report	30 April 2033

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

There are no post-authorization efficacy studies (PAES) which are specific obligations and/or conditions of the MAA.

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

RISK MINIMISATION PLAN

V.1. Routine Risk Minimisation Measures

The EU SmPC and package leaflet (PL) provide essential information to healthcare professionals and vaccine recipients on how Penbraya should be used, allowing for safe use.

Table 13. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
Use during pregnancy	Routine risk communication: • EU-SmPC Section 4.6 – Fertility, pregnancy and lactation • PL- Section 2 – Pregnancy and breast-feeding

V.2. Additional Risk Minimisation Measures

No additional risk minimisation measures are proposed.

V.3. Summary of Risk Minimisation Measures

Routine risk minimisation actions include the use of the SmPC and package leaflet (PL) to support the safe use of the vaccine. There are no additional risk minimisations measures proposed.

Table 14. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use during pregnancy	Routine risk minimisation measures: • SmPC section 4.6 – Fertility, pregnancy and lactation. • PL section 2 – Pregnancy and breast-feeding. Additional risk minimisation measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaires for safety concern (Pregnancy Follow-UP Questionnaire). • If Penbraya is used as part of a national immunisation programme or in a large outbreak situation, the MAH will review and summarize, in the PSUR, national surveillance data for IMD (serogroups A, B, C, W, Y), as available. Additional pharmacovigilance activities: • C3511007: A pregnancy registry study to evaluate the safety of PENBRAYA™ meningococcal vaccine exposure during pregnancy. • Final study report due date: 30 April 2033.

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Penbraya (MenABCWY)

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

Penbraya's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Penbraya should be used.

This summary of the RMP for Penbraya 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 Penbraya's RMP.

I. The Medicine and What It Is Used For

Penbraya is a vaccine indicated for active immunisation of individuals 10 years and older to prevent invasive disease caused by *Neisseria meningitidis* groups A, B, C, W, and Y. Each 0.5 mL dose of Penbraya contains 5 mcg of each conjugated polysaccharide of groups A, C, W, and Y (total of 20 mcg conjugates) and 60 mcg of each group B fHbp subfamily A and B (total of 120 mcg protein), 44 mcg of tetanus toxoid, 0.25 mg of AlPO4 as the active substances and it is given by intramuscular route of administration.

Further information about the evaluation of Penbraya's benefits can be found in Penbraya's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Penbraya, together with measures to minimise such risks and the proposed studies for learning more about Penbraya'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 events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Penbraya is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Penbraya 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 Penbraya. 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);

Table 15. List of Important Risks and Missing Information

Important identified risks	None
Important potential risks	None
Missing information	Use during pregnancy

II.B Summary of Important Risks and Missing Information

There are no identified or potential risks that are considered important for Penbraya.

Table 16. Missing Information: Use during pregnancy

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 – *Fertility, pregnancy and lactation.* PL*:* section 2 – *Pregnancy and breast-feeding*. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study C3511007: A pregnancy registry study to evaluate the safety of PENBRAYA™ meningococcal vaccine exposure during pregnancy. See section II.C of this summary for an overview of the post-authorisation development plan.

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 Penbraya.

II.C.2 Other Studies in Post-Authorisation Development Plan

C3511007: A pregnancy registry study to evaluate the safety of PENBRAYA™ meningococcal vaccine exposure during pregnancy.

Purpose of the study: to estimate the proportion of major congenital malformation (MCM), spontaneous abortion (SAB), elective termination, stillbirth, preterm birth, and small for gestational age (SGA) among individuals exposed to PENBRAYA during pregnancy or within 30 days prior to last menstrual period (LMP).

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Table of contents

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

EXPOSURE DURING PREGNANCY FOLLOW-UP QUESTIONNAIRE

EDP FU Questionnaire

**Merge this questionnaire with the appropriate Basic FU or Drug/Vaccine/Medical Device FU Questionnaire, and any other applicable questionnaires.*

Exposure During Pregnancy

1. According to the information provided, exposure to a product may have occurred during pregnancy or around the time of conception. Please confirm and complete all questions to the best of your ability and knowledge.

☐ Yes ☐ No ☐ Unknown

Maternal Obstetrical History

1. Occupation

_____

2. Was the mother previously pregnant?

☐ Yes ☐ No ☐ Unknown

If Yes, how many times:_____

3. Number of other children

_____

4. Outcome of previous pregnancies (e.g., live birth, miscarriage, elective termination, late fetal death, ectopic pregnancy, molar pregnancy)

_____

5. Did the mother experience previous pregnancy complications?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

6. Did the mother experience previous fetal/neonatal abnormalities?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

7. Does the mother have a history of sub-fertility?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

8. Was the mother treated for infertility?
☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

9. Mother's Relevant History (i.e., risk factors including environmental or occupational exposures (e.g., AIDS, toxins)).

10. Does the mother have a family history of congenital abnormality/ genetic diseases, and/or consanguinity (or any family relation or lineage) between parents?
☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

11. Results of serology tests (e.g., rubella, toxoplasmosis, etc.)

Maternal Information

1. Ante-natal check-up (e.g., fetal ultrasound, serum markers, etc.). Please specify dates in dd-Mmm-YYYY format and check-up results for this pregnancy.
_____

2. First day of last menstrual period (dd-Mmm-yyyy)
_____

3. Number of fetuses for this pregnancy
_____

4. Estimated delivery date for this pregnancy (dd-Mmm-yyyy)
_____

5. Gestational period at time of initial suspect drug exposure

_____ ☐ Trimester ☐ Month

6. Did the mother smoke during this pregnancy?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

7. Did the mother drink alcohol during this pregnancy?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

8. Did the mother use illicit drugs during this pregnancy?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

9. Did the mother experience any problems before delivery?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

10. Did the mother experience any problems during delivery (including delivery complications, fetal distress, amniotic fluid abnormal, abnormal placenta)?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

11. Did the mother experience any problems after delivery?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

12. Mode of delivery

☐ Vaginal ☐ Cesarean ☐ Unknown

13. Outcome of this pregnancy

- ☐ Full term live birth
- ☐ Premature live birth
- ☐ Post-mature live birth
- ☐ Stillbirth
- ☐ Late foetal death
- ☐ Ectopic pregnancy
- ☐ Molar pregnancy
- ☐ Spontaneous abortion/miscarriage
- ☐ Induced/elective abortion
- ☐ Unknown

14. Date of outcome of this pregnancy (dd-Mmm-yyyy)

_____

Neonatal Information

1. Sex (at birth)

☐ Male ☐ Female

2. Weight at birth (number and unit)

_____ ☐ kg ☐ lbs & oz

3. Length at birth (number and unit)

_____

4. Head circumference at birth (number and unit)

_____

5. Apgar score at 1 min

_____

6. Apgar score at 5 min

_____

7. Gestational age at birth in weeks

_____

8. Outcome of Fetus/Infant

- ☐ Healthy newborn
- ☐ Congenital malformation/anomaly (specify below)
- ☐ Other neonatal problem/abnormality (include dysmaturity, neonatal illness, hospitalization, drug therapies) (specify below)
- ☐ Intrauterine death
- ☐ Neonatal death
- ☐ Outcome pending (not born yet)
- ☐ Perinatal complications (specify below)
- ☐ Post-perinatal complications (specify below)
- ☐ Unknown

Please specify:

Paternal Information

1. Father's Age

_____ ☐ Years ☐ Months ☐ Days

Age Group:

☐ Adolescent (12-17 Years) ☐ Adult (18-64 Years) ☐ Elderly (65 or older)

2. Occupation

_____

3. Father's Relevant History (i.e., risk factors including environmental or occupational exposures (e.g., AIDS, toxins)).

4. Were any drugs (e.g., over-the-counter, medical prescription) taken by the father during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If yes, please specify:_____

5. Did the father smoke during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

6. Did the father drink alcohol during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

7. Did the father use illicit drugs during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

8. Does the father have a family history of congenital abnormality/ genetic diseases, and/or consanguinity (or any family relation or lineage) between parents?

☐ Yes ☐ No ☐ Unknown

If yes, please specify:_____

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

Not applicable.