

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

PENMENVY (Meningococcal Groups A, B, C, W, and Y Vaccine) for injectable suspension, for intramuscular use
Initial U.S. Approval: 2025

INDICATIONS AND USAGE

PENMENVY is a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroups A, B, C, W, and Y in individuals 10 through 25 years of age. (1)

DOSAGE AND ADMINISTRATION

For intramuscular use. (2)

- Administer 2 doses (approximately 0.5 mL each) of PENMENVY 6 months apart. (2.1)
- To prepare PENMENVY, reconstitute the Lyophilized MenACWY Component with the MenB Component. (2.2)

DOSAGE FORMS AND STRENGTHS

For injectable suspension. A single dose after reconstitution is approximately 0.5 mL. (3)

CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) to a previous dose of PENMENVY, to any component of this vaccine, or to any other diphtheria toxoid-containing vaccine. (4)

WARNINGS AND PRECAUTIONS

Syncope (fainting) has occurred in association with administration of PENMENVY. Procedures should be in place to avoid injury from fainting. (5.2)

ADVERSE REACTIONS

The most commonly reported ($\geq 10\%$) solicited adverse reactions after Dose 1 and Dose 2, respectively:

- in individuals aged 10 through 25 years were pain at the injection site (92% and 88%), fatigue (51% and 42%), headache (42% and 36%), myalgia (15% and 12%), nausea (15% and 10%), erythema (13% and 12%), and swelling (13% and 12%). (6.1)
- in MenACWY conjugate vaccine-experienced individuals aged 15 through 25 years were pain at the injection site (80% and 74%), headache (41% and 33%), fatigue (40% and 33%), myalgia (15% and 13%), and nausea (15% and 12%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2025

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PENMENVY is a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroups A, B, C, W, and Y in individuals 10 through 25 years of age.

2 DOSAGE AND ADMINISTRATION

For intramuscular use.

2.1 Dose and Schedule

Administer 2 doses (approximately 0.5 mL each) of PENMENVY 6 months apart.

2.2 Preparation

PENMENVY is supplied as one vial of Lyophilized MenACWY Component (powder) and one prefilled syringe of MenB Component (liquid) which must be combined before administration.

Use only the supplied MenB Component to reconstitute the Lyophilized MenACWY Component.

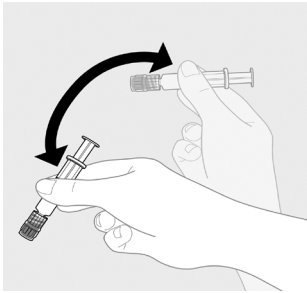


Figure 1. Invert the prefilled syringe of the MenB Component multiple times to form a homogeneous suspension. Do not use the prefilled syringe of the MenB Component if it cannot be resuspended.

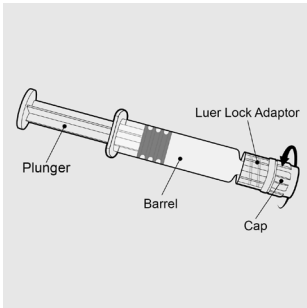


Figure 2. Hold the syringe by the barrel. Unscrew the syringe cap by twisting it counterclockwise.

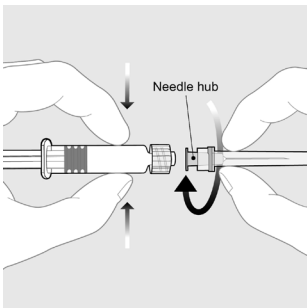


Figure 3. Connect the hub of a sterile needle to the Luer Lock Adaptor of the prefilled syringe of the MenB Component and rotate a quarter turn clockwise until it locks.

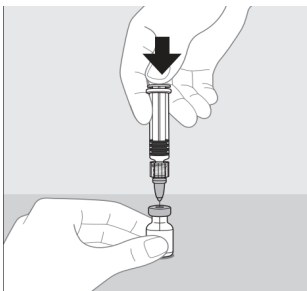


Figure 4. Cleanse the stopper of the vial containing the Lyophilized MenACWY Component. Slowly transfer the entire contents of the syringe into the vial containing the Lyophilized MenACWY Component.

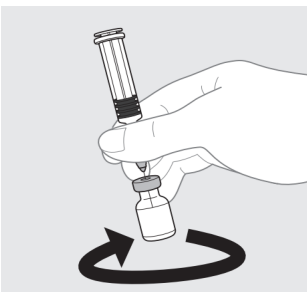


Figure 5. Without removing the needle from the vial, swirl the vial gently until powder is completely dissolved. Do not invert the vial or shake vigorously.

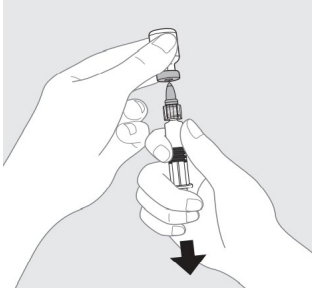


Figure 6. After reconstitution, invert the vial and withdraw the entire contents.

PENMENVY is a white opalescent suspension. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exist, PENMENVY should not be administered.

2.3 Administration

Administer intramuscularly.

Administer PENMENVY immediately after reconstitution.

3 DOSAGE FORMS AND STRENGTHS

For injectable suspension. A single dose after reconstitution is approximately 0.5 mL.

4 CONTRAINDICATIONS

Do not administer PENMENVY to individuals with a severe allergic reaction (e.g., anaphylaxis) to a previous dose of PENMENVY, to any component of this vaccine, or to any other diphtheria toxoid-containing vaccine [see Description (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Management of Allergic Reactions

Appropriate medical treatment must be immediately available to manage potential anaphylactic reactions following administration of PENMENVY.

5.2 Syncope

Syncope (fainting) has occurred in association with administration of PENMENVY. Procedures should be in place to avoid injury from fainting.

5.3 Limitation of Vaccine Effectiveness

Vaccination with PENMENVY may not protect all vaccine recipients. PENMENVY may not provide protection against all meningococcal serogroup B strains [see Clinical Pharmacology (12.1)].

5.4 Altered Immunocompetence

Reduced Immune Response

Immunocompromised persons, including those receiving immunosuppressive therapy, may have reduced immune responses to PENMENVY.

Complement Deficiency

Persons with certain complement deficiencies and persons receiving treatment that inhibits terminal complement activation are at increased risk for invasive disease caused by *N. meningitidis*, including disease caused by serogroups A, B, C, W, and Y, even if they develop antibodies following vaccination with PENMENVY [see *Clinical Pharmacology (12.1)*].

5.5 Guillain-Barré Syndrome

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

6 ADVERSE REACTIONS

The most commonly reported ($\geq 10\%$) solicited adverse reactions after Dose 1 and Dose 2, respectively, in Study 1 in participants aged 10 through 25 years (87% of whom were MenACWY conjugate vaccine-naïve) were pain at the injection site (92% and 88%), fatigue (51% and 42%), headache (42% and 36%), myalgia (15% and 12%), nausea (15% and 10%), erythema (13% and 12%), and swelling (13% and 12%).

The most commonly reported ($\geq 10\%$) solicited adverse reactions after Dose 1 and Dose 2, respectively, in Study 2 in MenACWY conjugate vaccine-experienced participants aged 15 through 25 years were pain at the injection site (80% and 74%), headache (41% and 33%), fatigue (40% and 33%), myalgia (15% and 13%), and nausea (15% and 12%).

6.1 Clinical Trials Experience

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

The safety of PENMENVY was evaluated in 12 clinical studies¹ in which a total of 3,718 participants received at least one dose of PENMENVY. Participants in Study 1 (aged 10 through 25 years) and Study 2 (aged 15 through 25 years) were scheduled to receive PENMENVY according to the approved dosing schedule (2 doses administered 6 months apart). Participants in the other studies may have received PENMENVY according to unapproved dosing schedules. Across the 12 studies, 2,969 participants received at least 1 dose of BEXSERO (Meningococcal Group B Vaccine) and 361 participants received a single dose of MENVEO [Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM₁₉₇ Conjugate Vaccine]. Across the studies, the median age was 16 years, males comprised 46%, and 86% of participants were White, 6% were Black, 4% were Asian, and 4% were of other racial groups. In these studies, 13% of participants were Hispanic. Approximately 35% of participants were from the U.S.

Nine of the 12 studies (including Study 1 and Study 2) collected non-serious unsolicited adverse events through 30 days after each vaccination, and the other 3 studies collected these events through 7 days after each vaccination. All studies collected serious adverse events through at least 1 month following the last vaccination. Study 1 and Study 2 collected serious adverse events through 12 months following the first vaccination and at least 5 months following the last vaccination.

Study 1 (NCT04502693) was a randomized, controlled, observer-blind study conducted in 7 countries (U.S., Australia, Canada, Czech Republic, Estonia, Finland, and Turkey). In this study, 1,657 participants aged 10 through 25 years received at least 1 dose of PENMENVY. Participants were scheduled to receive 2 doses of PENMENVY 6 months apart. Separate groups received BEXSERO either as a 0-, 2-, 6-month schedule or 0-, 6-month schedule. A single dose of MENVEO was administered 1 month after the third dose in the 0-, 2-, 6-month group and 2 months after the first dose of BEXSERO in the 0-, 6-month group (these participants received saline placebo at month 7). A separate group received a single dose of MENVEO at month 0, a saline placebo dose at month 2, and doses of BEXSERO at months 6 and 7 (an unapproved BEXSERO dosing regimen). All participants were MenB vaccine-naïve. Both MenACWY conjugate vaccine-naïve (87%) and MenACWY conjugate vaccine-experienced (13%, vaccinated at least 4 years prior to study enrollment) participants were part of the study. The median age was 16 years, males comprised 47%, and 89% of participants were White, 5% were Asian, 4% were Black, and 2% were of other racial groups. Among study participants, 5% were Hispanic. Approximately 30% of participants were from the U.S.

Study 2 (NCT04707391) was a randomized, controlled, observer-blind study conducted in 4 countries (U.S., Australia, Canada, and Argentina). In this study, 626 participants aged 15 through 25 years received at least 1 dose of PENMENVY. All participants were MenACWY conjugate vaccine-experienced (vaccinated at least 4 years prior to study enrollment). A separate group received a single dose of MENVEO followed 6 months later by 2 doses of BEXSERO administered 1 month apart (an unapproved BEXSERO dosing regimen). In this study, the median age was 16 years, males comprised 47%, and 75% of participants were White, 14% were Black, 6% were of other racial groups, and 4% were Asian. Among study participants, 30% were Hispanic. Approximately 59% of participants were from the U.S.

Solicited Adverse Reactions

In Study 1, solicited local and systemic adverse reactions were collected for 7 days after study vaccination using electronic diaries. The rates of local and systemic adverse reactions reported in Study 1 among participants aged 10 through 25 years following each dose of PENMENVY administered 6 months apart, each dose of BEXSERO administered 6 months apart, or a single dose of MENVEO are presented in Table 1.

Table 1. Percentage of Participants Aged 10 Through 25 Years Reporting Solicited Local and Systemic Adverse Reactions Within 7 Days of PENMENVY, BEXSERO, or MENVEO, by Dose in Study 1

Solicited Reaction ^a		PENMENVY		BEXSERO		MENVEO
		%		%		%
		Dose 1	Dose 2	Dose 1	Dose 2	Dose 1
		N = 1,638	N = 1,428	N = 894	N = 759	N = 178
Local Adverse Reactions						
Pain	Any	92	88	92	89	38
	Severe	6	7	6	8	0
Erythema	Any	13	12	10	12	6
	Severe	1	2	1	1	1
Swelling	Any	13	12	10	11	6
	Severe	2	2	1	2	1
Induration	Any	9	8	7	8	4
	Severe	1	1	2	1	0
Systemic Adverse Reactions						
Fatigue	Any	51	42	46	45	44
	Severe	3	3	1	3	2
Nausea	Any	15	10	12	11	15
	Severe	0.3	0.3	1	0.4	1
Myalgia	Any	15	12	12	14	7
	Severe	1	1	1	0.4	0
Arthralgia	Any	8	7	8	7	10
	Severe	1	0.4	0.3	0	0
Headache	Any	42	36	37	37	39
	Severe	2	1	1	1	2
Fever	Any	3	2	2	3	2
	Severe	0.1	0.1	0.1	0	1

Study 1: NCT04502693.

N = Number of participants in Solicited Safety Set (participants who received at least 1 dose of study vaccine who reported solicited safety data).

^a Erythema, swelling, and induration: Any (≥ 25 mm); Severe (> 100 mm). Pain, fatigue, nausea, myalgia, arthralgia, headache: Any includes Mild (transient with no limitation in normal daily activity), Moderate (some limitation in normal daily activity), and Severe (unable to perform normal daily activity). Fever: Any ($\geq 38.0^\circ\text{C}/100.4^\circ\text{F}$); Severe ($\geq 40.0^\circ\text{C}/104.0^\circ\text{F}$).

In Study 2, solicited local and systemic adverse reactions were collected for 7 days after study vaccination using electronic diaries. The rates of local and systemic adverse reactions reported in Study 2 among participants aged

15 through 25 years following each dose of PENMENVY administered 6 months apart or a single dose of MENVEO are presented in Table 2.

Table 2. Percentage of Participants Aged 15 Through 25 Years Reporting Solicited Local and Systemic Adverse Reactions Within 7 Days of PENMENVY or MENVEO, by Dose in Study 2

		PENMENVY		MENVEO
		%		%
Solicited Reaction ^a		Dose 1	Dose 2	Dose 1
		N = 608	N = 505-507	N = 600-601
Local Adverse Reactions				
Pain	Any	80	74	32
	Severe	3	3	0.3
Erythema	Any	5	6	2
	Severe	0.5	0.6	0
Swelling	Any	4	6	2
	Severe	0.3	0.6	0.3
Induration	Any	4	5	2
	Severe	2	0.6	0.2
Systemic Adverse Reactions				
Fatigue	Any	40	33	37
	Severe	1	2	0.5
Nausea	Any	15	12	13
	Severe	0.5	1	0.7
Myalgia	Any	15	13	11
	Severe	0.2	0.4	0.3
Arthralgia	Any	7	6	8
	Severe	0	0.2	0
Headache	Any	41	33	35
	Severe	1	1	0.7
Fever	Any	2	2	1
	Severe	0.2	0.4	0.2

Study 2: NCT04707391.

N = Number of participants in Solicited Safety Set (participants who received at least 1 dose of study vaccine who reported solicited safety data).

^a Erythema, swelling, and induration: Any (≥ 25 mm); Severe (> 100 mm). Pain, fatigue, nausea, myalgia, arthralgia, headache: Any includes Mild (transient with no limitation in normal daily activity), Moderate

(some limitation in normal daily activity), and Severe (unable to perform normal daily activity). Fever: Any ($\geq 38.0^{\circ}\text{C}/100.4^{\circ}\text{F}$); Severe ($\geq 40.0^{\circ}\text{C}/104.0^{\circ}\text{F}$).

Unsolicited Adverse Events

In an analysis across the 12 studies, unsolicited adverse events that were reported in participants who received PENMENVY (N = 3,718) and were determined to be causally related included syncope, dizziness, and pre-syncope (0.9%); lymphadenopathy (0.2%); and hypersensitivity (0.1%). The onset of syncope, dizziness, pre-syncope, and lymphadenopathy ranged from 1 to 30 days and the onset of hypersensitivity ranged from 9 to 27 days.

Serious Adverse Events

In Study 1, serious adverse events that occurred through 12 months following the first vaccination and at least 5 months following the last vaccination were reported by 1.5% of participants in the PENMENVY group (N = 1,648), 2.4% of participants in the group who received BEXSERO as a 0-, 6-month schedule with a dose of MENVEO at month 2 (N = 900), and 2.8% of participants in the group who received MENVEO at month 0 and BEXSERO at months 6 and 7 (N = 178).

In Study 2, serious adverse events that occurred through 12 months following the first vaccination and at least 5 months following the last vaccination were reported by 2.9% of participants in the PENMENVY group (N = 626) and 1.1% of participants in the group who received MENVEO at month 0 and BEXSERO at months 6 and 7 (N = 621).

Across the 12 clinical studies, serious adverse events were reported within 30 days after any dose by 0.6% of participants who received PENMENVY (N = 3,718), 0.4% of participants who received BEXSERO (N = 2,969), and 0.3% of participants who received MENVEO (N = 361). Two serious adverse events reported following administration of PENMENVY were assessed as vaccine-related and are described below.

In Study 3,¹ connective tissue disorder was reported in an adolescent participant who developed 3 episodes of petechiae (7 days after PENMENVY Dose 1, 18 days after PENMENVY Dose 2 [given 1 month after Dose 1], and 17 days after HAVRIX [Hepatitis A Vaccine]) and was diagnosed with a connective tissue disorder 44 days after PENMENVY Dose 2.

In Study 3,¹ seizures were reported in an adult participant with onset 9 hours after PENMENVY Dose 1.

6.2 Postmarketing Experience

The following adverse reactions have been reported during postapproval use of BEXSERO or MENVEO. The postmarketing safety experience with BEXSERO and MENVEO is relevant because PENMENVY contains the same group A, C, W, and Y CRM₁₉₇-conjugated oligosaccharide components and MenB recombinant protein components. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine exposure.

Blood and Lymphatic System Disorders

Lymphadenopathy.^{a,b}

Ear and Labyrinth Disorders

Hearing impaired,^b ear pain,^b vertigo,^b vestibular disorder.^b

Eye Disorders

Eyelid ptosis.^b

General Disorders and Administration Site Conditions

Injection site reactions (including injection site pruritus,^b pain,^b erythema,^b inflammation,^b swelling,^b extensive swelling of the vaccinated limb,^{a,b} blisters at or around the injection site,^a and injection site nodule which may persist for more than 1 month^a), fatigue,^b malaise,^b pyrexia.^b

Immune System Disorders

Allergic reactions,^a anaphylactic reactions,^a eye swelling,^a rash,^a hypersensitivity reactions,^b anaphylaxis.^b

Infections and Infestations

Vaccination site cellulitis.^b

Injury, Poisoning, and Procedural Complications

Fall,^b head injury.^b

Investigation

Alanine aminotransferase increased,^b body temperature increased.^b

Musculoskeletal and Connective Tissue Disorders

Arthralgia,^b bone pain.^b

Nervous System Disorders

Dizziness,^b syncope,^{a,b} tonic convulsion,^b headache,^b facial paresis,^b balance disorder,^b vasovagal responses to injection.^a

Respiratory, Thoracic, and Mediastinal Disorders

Oropharyngeal pain.^b

Skin and Subcutaneous Tissue Disorders

Skin exfoliation.^b

^a Observed with BEXSERO.

^b Observed with MENVEO.

Postmarketing Observational Safety Study

In a postmarketing observational safety study conducted in a U.S. health maintenance organization, data from electronic health records of 48,899 persons aged 11 through 21 years were used to evaluate pre-specified events of interest following vaccination with MENVEO. Using a self-controlled case series method, Bell's palsy showed a statistically significant increased risk in the period 1 to 84 days post vaccination compared with the control period, with an overall adjusted relative incidence of 2.9 (95% CI: 1.1-7.5). Among the 8 reported cases of Bell's palsy, 6 cases occurred in persons who received MENVEO concomitantly with one or more of the following vaccines: Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap), a human papillomavirus vaccine, and Influenza Vaccine. All reported Bell's palsy cases resolved.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

There are no adequate and well-controlled studies of PENMENVY in pregnant women. Available human data on PENMENVY administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

A developmental toxicity study was performed in female rabbits administered a dose of PENMENVY (0.5 mL) on 5 occasions, three times prior to mating and twice during gestation. This study revealed no vaccine-related effects on female fertility, fetal development or postnatal development (*see Data*).

Data

Animal Data: In a developmental toxicity study, female rabbits were administered a dose of PENMENVY (0.5 mL) by intramuscular injection on 5 occasions: 35, 21 and 7 days prior to mating, and on gestation days 7 and 20. No vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported in the study.

8.2 Lactation

Risk Summary

It is not known whether the vaccine components of PENMENVY are excreted in human milk. Available data are not sufficient to assess the effects of PENMENVY on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PENMENVY and any potential adverse effects on the breastfed child from PENMENVY or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of PENMENVY have not been established in children younger than 10 years of age.

8.5 Geriatric Use

Safety and effectiveness of PENMENVY in adults aged 65 years and older have not been established.

11 DESCRIPTION

PENMENVY (Meningococcal Groups A, B, C, W, and Y Vaccine) is a sterile injectable suspension for intramuscular use. The vaccine is supplied as one vial of Lyophilized MenACWY Component which is reconstituted at the time of use with the accompanying prefilled syringe of MenB Component.

The Lyophilized MenACWY Component contains *N. meningitidis* serogroups A, C, W, and Y oligosaccharides conjugated individually to *Corynebacterium diphtheriae* CRM₁₉₇ protein. The polysaccharides are produced by bacterial fermentation of *N. meningitidis* serogroups A, C, W, or Y. *N. meningitidis* serogroup A, C, W, and Y strains are each cultured and grown on Franz Complete medium and treated with formaldehyde. MenA, MenW,

and MenY polysaccharides are purified by several steps, including extraction, filtration, and precipitation. MenC polysaccharide is purified by a combination of extraction, chromatography, and precipitation steps.

The protein carrier (CRM₁₉₇) is produced by bacterial fermentation and is purified by a series of chromatography and ultrafiltration steps. The *C. diphtheriae* is cultured and grown on CY medium containing yeast extracts and amino acids.

The oligosaccharides are prepared for conjugation from the purified polysaccharides which are processed by hydrolysis, sizing, and reductive amination. After activation, each oligosaccharide is covalently linked to the CRM₁₉₇ protein. The resulting glycoconjugates are purified to yield the four drug substances, which are formulated with sucrose and phosphate and lyophilized to form the Lyophilized MenACWY Component. The Lyophilized MenACWY Component is a white to off-white lyophilized cake.

The MenB Component contains recombinant *N. meningitidis* proteins *Neisseria* adhesin A (NadA), Neisserial Heparin Binding Antigen (NHBA), and factor H binding protein (fHbp), and Outer Membrane Vesicles (OMV). The NadA component is a fragment of the full-length protein derived from *N. meningitidis* strain 2996 (peptide 8 variant 2/3).² The NHBA component is a recombinant fusion protein comprised of NHBA (peptide 2)² and accessory protein 953 derived from *N. meningitidis* strains NZ98/254 and 2996, respectively. The fHbp component is a recombinant fusion protein comprised of fHbp (variant 1.1)² and the accessory protein 936 derived from *N. meningitidis* strains MC58 and 2996, respectively. These 3 recombinant proteins are individually produced in *Escherichia coli* and purified through a series of column chromatography steps. The OMV antigenic component is produced by fermentation of *N. meningitidis* strain NZ98/254 (expressing outer membrane protein Porin A [PorA] serosubtype P1.4),³ followed by inactivation of the bacteria by deoxycholate, which also mediates vesicle formation. The antigens are adsorbed onto aluminum hydroxide. The MenB Component is a white opalescent suspension.

After reconstitution, each approximately 0.5-mL dose contains 10 mcg MenA oligosaccharide; 5 mcg of each of MenC, MenW, and MenY oligosaccharides; 25.4 to 65.8 mcg CRM₁₉₇ protein; 50 mcg each of recombinant proteins NadA, NHBA, and fHbp; and 25 mcg of OMV. Each dose also contains 1.5 mg aluminum hydroxide (0.5 mg of Al³⁺), 3.125 mg sodium chloride, 0.776 mg histidine, 22.5 mg sucrose, and ≤0.7 mg potassium phosphate salts. Each dose contains less than 0.01 mcg kanamycin (by calculation). Residual formaldehyde per dose is estimated to be not more than 0.30 mcg. After reconstitution, PENMENVY is a white opalescent suspension.

The tip cap and rubber plunger of the prefilled syringe and the stopper of the vial are not made with natural rubber latex.

PENMENVY does not contain preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Protection against invasive meningococcal disease is conferred mainly by complement-mediated antibody-dependent killing of *N. meningitidis* strains.⁴ Immunization with PENMENVY is intended to stimulate the production of antibodies with bactericidal activity specific to the capsular polysaccharides of *N. meningitidis* serogroups A, C, W, and Y and to the protein antigens NHBA, NadA, fHbp and OMV expressed by serogroup B meningococcal strains.

NHBA, NadA, and fHbp are proteins found on the surface of meningococci and contribute to the ability of the bacterium to cause disease. OMV derived from the bacterial outer membrane contains PorA and other surface proteins. The susceptibility of serogroup B meningococci to complement-mediated antibody-dependent killing following vaccination with PENMENY is dependent on both the antigenic similarity of the bacterial and vaccine antigens, as well as the amount of antigen expressed on the surface of the invading meningococci.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

PENMENY has not been evaluated for carcinogenic or mutagenic potential or impairment of male fertility in animals.

14 CLINICAL STUDIES

The effectiveness of PENMENY was assessed by measuring serum bactericidal activity (SBA) in an assay that used endogenous complement preserved in the serum samples collected from study participants (enc-hSBA) and an assay that used an exogenous source of human complement (hSBA).

The enc-hSBA assay was used to assess effectiveness against diverse *N. meningitidis* serogroup B strains. Participants' sera were tested for the presence or absence of bactericidal activity to measure breadth of immune response against a panel of 110 diverse U.S. disease-causing *N. meningitidis* serogroup B strains that were collected between 2000 and 2008. The panel includes most antigen types found among serogroup B isolates circulating in the U.S. between 2000 and 2017, and includes some strains with genetic profiles characterized as hypervirulent. Each participant's serum was tested at a four-fold dilution against a maximum of 35 strains randomly selected from the panel.

The hSBA assay measured bactericidal activity in participants' sera against the 5 *N. meningitidis* serogroups. For serogroup B, four meningococcal serogroup B indicator strains expressing different antigens (fHbp, NadA, NHBA and OMV) were utilized. For serogroups A, C, W, and Y, one strain was utilized per serogroup.

Breadth of Immune Response Elicited by PENMENY Against Serogroup B (enc-hSBA Assay)

Study 1 evaluated enc-hSBA responses in participants aged 10 through 25 years at one month after Dose 2 of PENMENY, after Dose 2 of the BEXSERO 0-, 6-month schedule, after Dose 3 of the BEXSERO 0-, 2-, 6-month schedule, and after a single dose of MENVEO, using responder-based and test-based analyses.

Responder-based analyses (Table 3) evaluated the percentages of participants whose sera killed $\geq 70\%$ of the tested strains.

Table 3. Percentage of Participants Whose Sera Killed $\geq 70\%$ of Meningococcal Serogroup B Strains Tested^a (Responder-Based) Following PENMENVY and BEXSERO, Study 1^b

Group^c	N	% Responders^d (95% CI)
PENMENVY	817	84.1 (81.4 ^e , 86.5)
BEXSERO (0, 6 Months)	813	89.8 (87.5, 91.8)
BEXSERO (0, 2, 6 Months)	790	93.4 (91.5, 95.0)

Study 1: NCT04502693.

N = Number of participants, CI = Confidence interval.

^a Each participant's serum was tested using the enc-hSBA assay for bactericidal activity (yes/no) against a maximum of 35 strains randomly selected from the 110-strain panel.

^b Full Analysis Set includes all participants who received at least 1 dose of the study treatment and have post-vaccination immunogenicity data.

^c enc-hSBA response was measured one month after Dose 2 of PENMENVY, one month after Dose 2 of BEXSERO (0-, 6-month schedule), or one month after Dose 3 of BEXSERO (0-, 2-, 6-month schedule).

^d % Responders is defined as percentages of participants whose serum kills $\geq 70\%$ of strains tested using the enc-hSBA assay.

^e Predefined criterion (lower limit of the 2-sided 95% CI $> 65\%$) met. CI calculated using Clopper-Pearson method.

Of the approximately 35 serogroup B strains tested per participant in the enc-hSBA assay at 1 month following vaccination, the median percentage killed by each participant's serum was 85.3% (25th percentile, 74.3%; 75th percentile, 91.4%) after Dose 2 of PENMENVY; 88.2% (25th percentile, 80.0%; 75th percentile, 94.3%) after Dose 2 of the 0-, 6-month BEXSERO schedule; 88.6% (25th percentile, 80.0%; 75th percentile, 94.3%) after Dose 3 of the 0-, 2-, 6-month BEXSERO schedule; and 17.1% (25th percentile, 11.1%; 75th percentile, 26.7%) after MENVEO.

Test-based analyses evaluated the percentage of tests with bactericidal activity. The non-inferiority criterion was met for the percentage of tests with bactericidal activity following PENMENVY compared with BEXSERO (0-, 6-month schedule) (Table 4).

Table 4. Percentages of Tests^a With Bactericidal Activity Against Meningococcal Serogroup B Strains Following PENMENVY, BEXSERO, and MENVEO, Study 1^b

Group^c	Number of Participants	% of Tests with Bactericidal Activity (n/N)	Percent Difference PENMENVY – BEXSERO (0, 6 Months) (95% CI)^d
PENMENVY	754	82.5 (21,222 / 25,715)	-3.0 (-3.7 ^e , -2.4)
BEXSERO (0, 6 Months)	764	85.6 (22,365 / 26,142)	
BEXSERO (0, 2, 6 Months)	747	86.7 (22,184 / 25,596)	-
MENVEO	133	21.0 (918 / 4,374)	-

Study 1: NCT04502693.

n = Number of tests with bactericidal activity, N = Total number of tests, CI = Confidence interval.

^a Each test qualitatively assessed (yes/no) the bactericidal activity of one participant's serum using the enc-hSBA assay against one of the 110 U.S. meningococcal serogroup B strains. Each participant's serum was tested against a maximum of 35 strains randomly selected from the 110-strain panel.

^b Per Protocol Set includes all participants in the Full Analysis Set minus participants with protocol deviations that lead to exclusion from the Per Protocol Set.

^c enc-hSBA responses were measured one month after Dose 2 of PENMENVY, one month after Dose 2 of BEXSERO (0-, 6-month schedule), one month after Dose 3 of BEXSERO (0-, 2-, 6-month schedule), or one month after a single dose of MENVEO.

^d Predefined non-inferiority criterion was defined as lower limit of the 2-sided 95% CI for vaccine group differences [PENMENVY minus BEXSERO (0-, 6-month schedule)] above -5%. Criterion for non-inferiority of PENMENVY to more than one comparator with respect to percent of tests with bactericidal activity was not pre-specified.

^e Met predefined non-inferiority criterion. CI calculated using Miettinen and Nurminen method.

For each individual strain in the 110-strain panel, the percentage of tests with bactericidal activity following PENMENVY ranged from 2% to 100%; the median was 97% (25th percentile, 70%; 75th percentile, 99%). For each individual strain, the percentage of tests with bactericidal activity following BEXSERO ranged from 4% to 100%; the median was 97% (25th percentile, 80%; 75th percentile, 99%) for the 0-, 6-month schedule and 98% (25th percentile, 85%; 75th percentile, 99%) for the 0-, 2-, 6-month schedule. For each individual strain, the percentage of tests with bactericidal activity following MENVEO ranged from 0% to 100%; the median was 12% (25th percentile, 3%; 75th percentile, 28%).

Immune Response to PENMENVY Against Serogroup B (hSBA Assay)

In Study 1, immune responses in participants aged 10 through 25 years were measured at one month after Dose 2 of PENMENVY, after Dose 2 of the BEXSERO 0-, 6-month schedule, and after Dose 3 of the BEXSERO 0-, 2-, 6-month schedule with hSBA assays using indicator strains representative of each of the 4 antigenic components of PENMENVY (fHbp, NadA, NHBA, and OMV). The percentages of participants who achieved a 4-fold or greater increase in hSBA titer for each of the 4 strains (seroresponse) and the percentages

of participants with a titer greater than or equal to the lower limit of quantitation (LLOQ) of the assay for all 4 strains (composite response) are shown in Table 5.

Non-inferiority of PENMENVY compared with BEXSERO (0-, 6-month schedule) for the proportion of participants with a seroresponse was demonstrated for meningococcal serogroup B indicator strains for fHbp and NadA, but not for indicator strains for NHBA or OMV (Table 5).

Table 5. Percentages of Participants With hSBA Seroresponse and Composite Response Against Meningococcal Serogroup B Indicator Strains Following PENMENVY and BEXSERO, Study 1^a

% Seroresponse (95% CI)^{b,c,d,e}			
Antigen (Indicator Strain)	PENMENVY	BEXSERO (0, 6 Months)	Percent Difference PENMENVY – BEXSERO
fHbp (M14459)	N = 675 73.2 (69.7, 76.5)	N = 654 78.1 (74.8, 81.2)	-5.0 (-9.6 ^f , -0.3)
NadA (96217)	N = 671 92.7 (90.5, 94.5)	N = 655 95.9 (94.1, 97.3)	-3.2 (-5.8 ^f , -0.7)
NHBA (M13520)	N = 678 61.8 (58.0, 65.5)	N = 659 69.7 (66.0, 73.1)	-7.9 (-12.9 ^g , -2.8)
OMV (NZ98/254)	N = 642 42.2 (38.4, 46.1)	N = 624 58.3 (54.4, 62.2)	-16.1 (-21.5 ^g , -10.6)
% Composite Response (95% CI)^{d,e,h,i,j}			
Timepoint	PENMENVY	BEXSERO (0, 6 Months)	-
Baseline (pre-vaccination)	N = 747 1.1 (0.5, 2.1)	N = 708 0.6 (0.2, 1.4)	-
1 Month post-dose 2	N = 707 70.0 (66.5, 73.4)	N = 683 80.1 (76.9, 83.0)	-

Study 1: NCT04502693.

hSBA = Serum bactericidal activity measured using an exogenous source of human complement, CI = Confidence interval, fHbp = Factor H binding protein, N = Number of participants, NadA = *Neisseria* adhesin A, NHBA = Neisserial Heparin Binding Antigen, OMV = Outer Membrane Vesicles, LOD = Limit of detection, LLOQ = Lower limit of quantitation.

- ^a hSBA responses were measured one month after Dose 2 of PENMENVY or one month after Dose 2 of BEXSERO (0-, 6-month schedule).
- ^b Per Protocol Set includes all participants in the Full Analysis Set minus participants with protocol deviations that lead to exclusion from the Per Protocol Set.
- ^c Seroresponse is defined as: a post-vaccination hSBA titer at least 4-fold the LOD or \geq LLOQ, whichever is greater, for participants with pre-vaccination hSBA titer $<$ LOD, a post-vaccination hSBA titer at least 4-fold the LLOQ for participants with pre-vaccination hSBA titer \geq LOD and $<$ LLOQ, and a post-vaccination hSBA titer at least 4-fold the pre-vaccination hSBA titer for participants with pre-vaccination hSBA titer \geq LLOQ.
- ^d LOD = 4 for fHbp; 6 for NadA; 4 for NHBA; 4 for OMV. LLOQ = 5 for fHbp; 14 for NadA; 6 for NHBA; 6 for OMV.
- ^e CI calculated using Clopper-Pearson method.
- ^f Met predefined non-inferiority criterion (lower limit of the 2-sided 95% CI above -10% for vaccine group differences [PENMENVY minus BEXSERO (0-, 6-month schedule)]). CI calculated using Miettinen and Nurminen method.
- ^g Did not meet predefined non-inferiority criterion (lower limit of the 2-sided 95% CI below -10% for vaccine group differences [PENMENVY minus BEXSERO (0-, 6-month schedule)]). CI calculated using Miettinen and Nurminen method.
- ^h Full Analysis Set includes all participants who received at least 1 dose of the study treatment and have post-vaccination immunogenicity data.
- ⁱ Composite Response is defined as hSBA \geq LLOQ for all 4 meningococcal B indicator strains.
- ^j Criterion for non-inferiority of PENMENVY to BEXSERO (0-, 6-month schedule) with respect to the composite response was not pre-specified.

The percentages of participants with seroresponses after Dose 3 of BEXSERO (0-, 2-, 6-month schedule) were 81.1% (95% CI: 77.8, 84.1) for fHbp; 98.8% (95% CI: 97.6, 99.5) for NadA; 66.4% (95% CI: 62.6, 70.0) for NHBA; 56.4% (95% CI: 52.3, 60.4) for OMV (Per Protocol Set). The composite response at baseline and 1 month after dose 3 was 1.1% (95% CI: 0.5, 2.2.) and 81.5% (95% CI: 78.3, 84.4), respectively (Full Analysis Set).

Immune Response to PENMENVY Against Serogroups A, C, W, and Y (hSBA Assay)

The serum bactericidal antibody responses were measured using hSBA assay against serogroups A, C, W, and Y in MenACWY vaccine-naïve participants in Study 1 and in MenACWY vaccine-experienced participants in Study 2.

The non-inferiority criteria for the percentages of participants achieving a seroresponse against each of the four serogroups A, C, W, and Y were met at one month after Dose 2 of PENMENVY compared to a single dose of MENVEO in MenACWY vaccine-naïve participants (Table 6) and in MenACWY vaccine-experienced participants (Table 7).

Table 6. Percentages of Participants With hSBA Seroresponses Against Meningococcal Serogroups A, C, W, and Y Strains Following PENMENVY and MENVEO, MenACWY-Naïve, Study 1^{a,b}

Serogroup	% Seroresponse ^{c,d} (95% CI) ^e		Percent Difference PENMENVY – MENVEO (95% CI)
	PENMENVY	MENVEO	
A	N = 1,170 96.8 (95.7, 97.8)	N = 111 85.6 (77.6, 91.5)	11.3 (5.8 ^f , 19.0)
C	N = 1,189 97.2 (96.1, 98.1)	N = 114 50.0 (40.5, 59.5)	47.2 (38.1 ^f , 56.3)
W	N = 1,185 97.0 (95.9, 97.9)	N = 115 61.7 (52.2, 70.6)	35.3 (26.9 ^f , 44.5)
Y	N = 1,196 96.7 (95.6, 97.7)	N = 119 69.7 (60.7, 77.8)	27.0 (19.4 ^f , 35.8)

Study 1: NCT04502693.

hSBA = Serum bactericidal activity measured using an exogenous source of human complement, CI = Confidence interval, N = Number of participants, LOD = Limit of detection, LLOQ = Lower limit of quantitation.

^a Per Protocol Set includes all participants in the Full Analysis Set minus participants with protocol deviations that lead to exclusion from the Per Protocol Set.

^b Immune responses were measured one month after Dose 2 of PENMENVY or a single dose of MENVEO relative to baseline.

^c Seroresponse is defined as: a post-vaccination hSBA titer at least 4-fold the LOD for participants with pre-vaccination hSBA titer <LOD, a post-vaccination hSBA titer at least 4-fold the LLOQ for participants with pre-vaccination hSBA titer ≥LOD and <LLOQ, and a post-vaccination hSBA titer at least 4-fold the pre-vaccination hSBA titer for participants with pre-vaccination hSBA titer ≥LLOQ.

^d LOD = 5 for MenA; 4 for MenC, MenW, and MenY. LLOQ = 12 for MenA; 8 for MenC; 8 for MenW; 10 for MenY.

^e CI calculated using Clopper-Pearson method.

^f Met predefined non-inferiority criterion (lower limit of the 2-sided 95% CI above -10% for vaccine group differences [PENMENVY minus MENVEO]). CI calculated using Miettinen and Nurminen method.

Table 7. Percentages of Participants With hSBA Seroresponses Against Meningococcal Serogroups A, C, W, and Y Strains Following PENMENVY and MENVEO, MenACWY-Experienced, Study 2^{a,b}

Serogroup	% Seroresponse ^{c,d} (95% CI) ^e		Percent Difference PENMENVY – MENVEO (95% CI)
	PENMENVY	MENVEO	
A	N = 168 95.8 (91.6, 98.3)	N = 501 95.2 (93.0, 96.9)	0.6 (-3.8 ^f , 3.8)
C	N = 181 94.5 (90.1, 97.3)	N = 546 94.0 (91.6, 95.8)	0.5 (-4.1 ^f , 4.0)
W	N = 181 95.6 (91.5, 98.1)	N = 544 93.9 (91.6, 95.8)	1.6 (-2.7 ^f , 4.9)
Y	N = 180 95.0 (90.7, 97.7)	N = 537 94.4 (92.1, 96.2)	0.6 (-3.9 ^f , 3.9)

Study 2: NCT04707391.

hSBA = Serum bactericidal activity measured using an exogenous source of human complement,

CI = Confidence interval, N = Number of participants, LOD = Limit of detection, LLOQ = Lower limit of quantitation.

^a Per Protocol Set includes all participants in the Full Analysis Set minus participants with protocol deviations that lead to exclusion from the Per Protocol Set.

^b Immune responses were measured one month after Dose 2 of PENMENVY or a single dose of MENVEO relative to baseline.

^c Seroresponse is defined as: a post-vaccination hSBA titer at least 4-fold the LOD for participants with pre-vaccination hSBA titer <LOD, a post-vaccination hSBA titer at least 4-fold the LLOQ for participants with pre-vaccination hSBA titer ≥LOD and <LLOQ, and a post-vaccination hSBA titer at least 4-fold the pre-vaccination hSBA titer for participants with pre-vaccination hSBA titer ≥LLOQ.

^d LOD = 5 for MenA; 4 for MenC, MenW, and MenY. LLOQ = 12 for MenA; 8 for MenC; 8 for MenW; 10 for MenY.

^e CI calculated using Clopper-Pearson method.

^f Met predefined non-inferiority criterion (lower limit of the 2-sided 95% CI above -10% for vaccine group differences [PENMENVY minus MENVEO]). CI calculated using Miettinen and Nurminen method.

15 REFERENCES

1. Study 1 (NCT04502693), Study 2 (NCT04707391), Study 3 (NCT02212457), Study 4 (NCT02451514), Study 5 (NCT01272180), Study 6 (NCT01992536), Study 7 (NCT02946385), Study 8 (NCT02140762), Study 9 (NCT02285777), Study 10 (NCT01210885), Study 11 (NCT01367158), Study 12 (GSK Study V102P1)

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

PENMENVY is supplied in cartons containing:

- 10 vials of Lyophilized MenACWY Component (powder) and
- 10 prefilled TIP-LOK syringes (Luer Lock syringes) of MenB Component (liquid) packaged without needles.

TIP-LOK syringes are to be used with Luer Lock compatible needles.

The tip cap and rubber plunger of the prefilled syringe and the stopper of the vial are not made with natural rubber latex.

Table 8. Product Presentation for PENMENVY

Presentation	Carton NDC Number	Components	
		Lyophilized MenACWY Component (powder)	MenB Component (liquid)
Carton of 10 doses	NDC 58160-757-15	10 Vials NDC 58160-730-03	10 Prefilled syringes NDC 58160-750-03

16.2 Storage Before Reconstitution

Store refrigerated, away from the freezer compartment, at 36°F to 46°F (2°C to 8°C).

Store in the original carton to protect from light.

Do not freeze. Discard if the carton has been frozen.

16.3 Storage After Reconstitution

Use immediately after reconstitution.

17 PATIENT COUNSELING INFORMATION

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

Provide the following information to the vaccine recipient, parent, or guardian:

- Potential benefits and risks of immunization with PENMENVY.

- The importance of completing the immunization series.
- Potential for adverse reactions that have been temporally associated with administration of PENMENVY or other vaccines containing similar components.
- Advise them to report any adverse reactions to their healthcare provider, to GlaxoSmithKline at 1-888-825-5249, or through the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967 (or online at www.vaers.hhs.gov).

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