PRODUCT MONOGRAPH

NIMENRIX®

Meningococcal polysaccharide groups A, C, W-135 and Y conjugate vaccine

Powder and diluent for solution for injection

Active Immunizing Agent

Pfizer Canada ULC
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Kirkland, Quebec H9J 2M5

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular Injection	Powder and diluent for solution for injection *Neisseria meningitidis* serogroup A polysaccharide[1] 5 micrograms *Neisseria meningitidis* serogroup C polysaccharide[1] 5 micrograms *Neisseria meningitidis* serogroup W-135 polysaccharide[1] 5 micrograms *Neisseria meningitidis* serogroup Y polysaccharide[1] 5 micrograms	Sucrose Trometamol Sodium chloride *For a complete listing see Dosage Forms, Composition and Packaging section.*

[1] conjugated to tetanus toxoid carrier protein 44 micrograms

DESCRIPTION

NIMENRIX (meningococcal polysaccharide groups A, C, W-135 and Y conjugate vaccine) is a tetravalent meningococcal polysaccharide conjugated vaccine consisting of *Neisseria meningitidis* capsular polysaccharides A, C, W-135 and Y each coupled to tetanus toxoid as a carrier protein. The *Neisseria meningitidis* serogroups A and C polysaccharides are conjugated with an adipic dihydrazide (AH) spacer and indirectly conjugated to the tetanus toxoid whereas the W-135 and Y polysaccharides are conjugated directly to tetanus toxoid.

The vaccine does not contain any preservatives or adjuvants.

INDICATIONS AND CLINICAL USE

NIMENRIX is indicated for the active immunization of individuals from 6 weeks to 55 years of age against invasive meningococcal diseases caused by *Neisseria meningitidis* serogroups A, C, W-135 and Y.

CONTRAINDICATIONS

NIMENRIX should not be administered to subjects with known hypersensitivity to any component of the vaccine. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section.

WARNINGS AND PRECAUTIONS

General

NIMENRIX should under no circumstances be administered intravascularly, intradermally or subcutaneously.

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

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

Although NIMENRIX contains tetanus toxoid, this vaccine does not substitute for tetanus immunization.

Intercurrent Illness

As with other vaccines, vaccination with NIMENRIX should be postponed in subjects suffering from an acute severe febrile illness. The presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

Syncope

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Thrombocytopenia and Coagulation Disorders

As with other vaccines administered intramuscularly, NIMENRIX should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

Immunodeficiency

It may be expected that in patients receiving immunosuppressive treatment or patients with immunodeficiency, an adequate immune response may not be elicited.

Individuals with certain complement deficiencies and individuals receiving treatment that inhibits terminal complement activation (for example, eculizumab) are at increased risk for invasive disease caused by meningococcal polysaccharide serogroups A, C, W-135 and Y even if they develop antibodies following vaccination with NIMENRIX.

Safety and immunogenicity have not been assessed in patients with increased susceptibility to meningococcal infection due to conditions such as terminal complement deficiencies and anatomic or functional asplenia. In these individuals, an adequate immune response may not be elicited.

Protection Against Meningococcal Disease

NIMENRIX will only confer protection against *Neisseria meningitidis* serogroups A, C, W-135 and Y. The vaccine will not protect against other *Neisseria meningitidis* serogroups.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

Immune responses in toddlers aged 12-14 months

At one month post-dose, toddlers aged 12-14 months had similar rabbit complement serum bactericidal assay (rSBA) responses to groups A, C, W-135 and Y following one dose of NIMENRIX or two doses of NIMENRIX given two months apart.

A single dose was associated with lower human complement serum bactericidal assay (hSBA) titres to groups W-135 and Y compared with two doses given two months apart. Similar responses to groups A and C were observed after one or two doses (see CLINICAL TRIALS - Immunogenicity in toddlers aged 12-23 months). The clinical relevance of the findings is unknown. If a toddler is expected to be at particular risk of invasive meningococcal disease due to exposure to groups W-135 and Y, consideration may be given to administering a second dose after an interval of 2 months. Regarding waning of antibody against MenA or MenC after a first dose of NIMENRIX in children aged 12-23 months, see WARNINGS AND PRECAUTIONS - Persistence of serum bactericidal antibody titres.

Persistence of serum bactericidal antibody titres

Persistence of antibodies has been evaluated up to 5 years after vaccination. The persistence studies with NIMENRIX have shown a waning of serum bactericidal antibody titres against MenA when using human complement in the assay (hSBA) (see CLINICAL TRIALS – Persistence of Immune Response). The clinical relevance of the waning of hSBA MenA antibody titres is unknown. Currently there is limited information available on the safety of a booster dose. However, if an individual is expected to be at particular risk of exposure to MenA and received a dose of NIMENRIX more than approximately one year previously, consideration may be given to administering a booster dose.

Similar to the monovalent Men C comparator, a decline in antibody titres over time has been observed. The clinical relevance of the waning antibody titres is unknown. A booster dose might

be considered in individuals vaccinated at toddler age remaining at high risk of exposure to meningococcal disease caused by groups A, C, W-135 and Y (see CLINICAL TRIALS – Booster Response).

Special Populations

Pregnant Women: There is limited experience with use of NIMENRIX in pregnant women.

Animal studies with NIMENRIX do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryo/fetal development, parturition or post-natal development (see TOXICOLOGY).

NIMENRIX should be used during pregnancy only when clearly needed, and the possible advantages outweigh the potential risks for the fetus.

Nursing Women: The safety of NIMENRIX when administered to breastfeeding women has not been evaluated. It is unknown whether NIMENRIX is excreted in human breast milk.

NIMENRIX should only be used during breast-feeding when the possible advantages outweigh the potential risks.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety profile is based on two data sets:

- A pooled analysis on 9,621 subjects who have been vaccinated with one dose of NIMENRIX in clinical studies. The pooled analysis includes data for 3,079 toddlers (12 months to 23 months), 1,899 children (2 to 10 years), 2,317 adolescents (11 to 17 years) and 2,326 adults (18 – 55 years). In addition, a descriptive study provides safety data from 274 individuals aged 56 years and older and who have been vaccinated with one dose of NIMENRIX.
- Data from approximately 1000 infants (6 weeks to 12 months of age) who have been primed and boosted with NIMENRIX.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Solicited Adverse Reactions:

Infants 6 weeks to 12 months old

In Study MenACWY-TT-083, healthy infants received a primary series of 2 doses (at 2 and 4 months of age) of NIMENRIX or control vaccine (meningococcal group C CRM_{197}-conjugate vaccine [MenC-CRM] or meningococcal group C tetanus toxoid conjugate vaccine [MenC-TT]), with the first dose administered between 6 and 12 weeks of age, followed by a booster dose at 12 months of age. Routinely used infant vaccines DTaP-HBV-IPV/Hib and a 10-valent pneumococcal vaccine (PCV10) were coadministered. Table 1 presents the rates of solicited symptoms reported during the 4-day post-vaccination period.

Table 1 Study MenACWY-TT-083: Percentage of subjects with solicited local and general symptoms reported during the 4-day (Days 0-3) post-vaccination period (Primary and Booster Total Vaccinated cohorts)

	Type	NIMENRIX			MenC-CRM			MenC-TT		
		Dose 1 N=523	Dose 2 N=516	Booster N=510	Dose 1 N=509	Dose 2 N=507	Booster N=496	Dose 1 N=517	Dose 2 N=508	Booster N=503
Local Symptoms, %										
Pain	All	29.6	24.0	39.8	31.0	25.4	40.9	30.4	28.1	36.0
	Grade 3	3.3	2.1	4.5	2.4	1.8	6.3	4.6	2.4	3.6
Redness	All	24.5	32.6	43.3	27.1	42.2	42.9	27.1	38.8	45.3
	> 30 mm	0.2	0.0	1.2	0.4	0.0	1.0	0.2	0.2	0.8
Swelling	All	11.9	22.3	29.8	17.1	27.0	31.7	15.7	25.6	32.4
	> 30 mm	0.0	0.2	0.4	0.6	0.0	0.4	0.0	0.8	1.0
General Symptoms, %*										
	Type	**NIMENRIX**			**MenC-CRM**			**MenC-TT**		
		Dose 1 N=523	**Dose 2 N=516**	**Booster N=510**	**Dose 1 N=508**	**Dose 2 N=505**	**Booster N=496**	**Dose 1 N=517**	**Dose 2 N=507**	**Booster N=504**
Drowsiness	All	52.8	36.0	39.2	55.9	38.8	40.3	57.3	37.5	38.5
	Grade 3	4.2	1.4	1.8	3.1	2.2	3.6	6.2	2.6	2.6
Irritability	All	62.9	52.3	56.7	68.3	52.9	56.9	68.5	50.7	57.5
	Grade 3	7.6	5.4	6.3	7.7	6.3	7.1	9.7	7.5	7.7
Loss of appetite	All	38.4	33.1	36.3	37.4	29.7	38.1	41.4	29.6	37.3
	Grade 3	1.9	1.9	3.5	1.6	1.8	3.6	1.4	1.8	4.4
Fever (Rectally)	All ($\geq$38°C)	30.6	22.7	32.4	32.9	19.8	35.5	34.6	20.9	31.0
	>40°C	0	0.2	0.4	0	0.2	0.4	0	0.2	1.0

N= number of subjects with at least one documented dose. Doses 1 and 2 given at 2 and 4 months of age, respectively. Booster dose given at 12 months of age.

%= percentage of subjects reporting the symptom at least once

*Incidence of general symptoms reported for meningococcal vaccine (NIMENRIX, MenC-CRM or MenC-TT) coadministered with DTaP-HBV-IPV-Hib and PCV10

Toddlers 12 to 23 months old

In Study MenACWY-TT-039, healthy children 12 through 23 months of age were administered one dose of NIMENRIX either alone or co-administered with a first dose of PRIORIX-TETRA®, 1 dose of PRIORIX-TETRA or 1 dose of a licensed MenC-CRM_{197} (MenC-CRM) vaccine.

Table 2 presents the rates of solicited symptoms reported during the 4-day post-vaccination period in the Co-administered (Co-ad), NIMENRIX, PRIORIX-TETRA and MenC-CRM groups.

Table 2 Study MenACWY-TT-039: Percentage of subjects with solicited local and general symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort)

	Type	NIMENRIX + PRIORIX-TETRA N=375	NIMENRIX N=367	PRIORIX-TETRA N=124	MenC-CRM N=123
Local Symptoms, %					
Pain	All	24.3	29.2	17.7	25.2
	Grade 3	0.3	0.8	0.0	0.0
Redness	All	35.5	37.1	38.7	31.7
	> 30 mm	1.9	4.4	0.0	0.0
Swelling	All	13.9	18.8	5.6	8.1
	> 30 mm	2.4	4.1	0.0	0.0
General Symptoms, %					
	Type	**NIMENRIX + PRIORIX-TETRA N=375**	**NIMENRIX N=367**	**PRIORIX-TETRA N=124**	**MenC-CRM N=124**
Drowsiness	All	32.5	28.1	23.4	32.3
	Grade 3	0.3	0.0	0.8	0.0
Fever (Rectally)	All ($\geq$38^{o}C)	14.9	9.3	11.3	12.9
	>40^{o}C	0.0	0.0	0.8	0.0
Irritability	All	50.7	40.9	38.7	43.5
	Grade 3	0.8	0.5	1.6	0.0
Loss of appetite	All	28.5	22.9	23.4	26.6
	Grade 3	0.3	0.0	0	0.0

N= number of subjects with the dose documented
%= percentage of subjects reporting the symptom at least once

Redness was the most frequently reported solicited local symptom in each group after each vaccination (38.7% in the PRIORIX-TETRA group, 35.5% in the Co-ad group and 37.1% in the NIMENRIX group and 31.7% in the MenC-CRM group).

Irritability was the most frequently reported solicited general symptom in the 4 groups (50.7% in the Co-ad group, 40.9% in the NIMENRIX group, 38.7% in the PRIORIX-TETRA group and 43.5% in the MenC-CRM group).

In Study Men ACWY-TT-104, toddlers 12-14 months of age were vaccinated with either a single dose of NIMENRIX or 2 NIMENRIX doses administered 2 months apart. In the group who received 2 doses, the first and second doses were associated with similar local and systemic reactogenicity.

Children (2-10 years old), Adolescents (10-25 years old), and Adults (18-55 years old)

Children (2-5 years old)
In Study MenACWY-TT-081, healthy children aged 2 through 10 years of age were administered 1 dose of NIMENRIX or 1 dose of a licensed MenC-CRM vaccine.

Table 3 presents the percentage of subjects (aged 2 through 5 years of age) with solicited adverse reactions during the 4-day post vaccination period in the NIMENRIX and MenC-CRM groups.

Table 3 MenACWY-TT-081: Percentage of subjects with solicited local and general symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort), subjects 2 through 5 years of age

	Type	NIMENRIX N=162	MenC-CRM N=53
Local Symptoms, %			
Pain	All	27.8	28.3
	Grade 3	0.0	1.9
Redness	All	35.2	39.6
	>30 mm	6.8	15.1
Swelling	All	26.5	24.5
	>30 mm	4.3	5.7
General Symptoms, %			
Drowsiness	All	14.2	11.3
	Grade 3	0.0	1.9
Fever/(Orally)	All (≥37.5°C)	5.6	5.7
	>39.5°C	0.0	0.0
Irritability	All	15.4	11.3
	Grade 3	0.6	1.9
Loss of Appetite	All	10.5	9.4
	Grade 3	0.0	0.0

N= number of subjects with the dose documented
%= percentage of subjects reporting the symptom at least once

Redness was the most frequently reported solicited local symptom in each group (35.2% and 39.6% of the subjects in the NIMENRIX group and MenC-CRM group, respectively).

Irritability was the most frequently reported solicited general symptom in each group (15.4% and 11.3% of the subjects in the NIMENRIX group and MenC-CRM group, respectively). Drowsiness was also reported by 11.3% of the subjects in the MenC-CRM group, as compared to 14.2% of the subjects in the NIMENRIX group. Fever ≥ 37.5°C was reported by 5.6% of the subjects in the NIMENRIX group and 5.7% of the subjects in the MenC-CRM. The majority of fevers were measured by the rectal route (66.7% in the NIMENRIX group and 100% in the MenC-CRM group).

Children aged 6-10 years
Table 4 includes the percentage of subjects (aged 6 through 10 years of age) with solicited adverse reactions during the 4-day post vaccination period in the NIMENRIX and MenC-CRM groups.

Pain was the most frequently reported solicited local symptom in each group (43.9% and 54.0% of the subjects in the NIMENRIX group and MenC-CRM group, respectively).

Fatigue was the most frequently reported solicited general symptom in each group (22.3% and 22.0% of the subjects in the NIMENRIX group and MenC-CRM group, respectively). Fever ≥ 37.5°C was reported in 6.8% of the subjects in the NIMENRIX group and 2.0% of the subjects in the MenC-CRM group.

Adolescents aged 10-25 years
In Study MenACWY-TT-071, healthy subjects aged 10 through 25 years of age were administered 1 dose of NIMENRIX or 1 dose of MENACTRA® (ACWY-DT vaccine).

Table 4 includes the percentage of subjects (aged 10 through 25 years of age) with solicited adverse reactions during the 4-day post vaccination period in the NIMENRIX and MENACTRA groups.

The most common solicited local symptom during the 4-day post-vaccination period was pain at the injection site, reported by 51.4% and 55.4% of subjects in the NIMENRIX and MENACTRA groups, respectively. A much smaller percentage of these subjects reported pain with grade 3 intensity, ranging between 0.6% and 2.4% across all vaccine groups.

The incidence of redness at the injection site was 25.8% and 20.3% of subjects in the NIMENRIX and MENACTRA groups, respectively. The incidence of swelling was 19.1% and 13.5% of subjects, respectively. The majority of these events were grade 1 in intensity. Grade 3 events of redness (i.e. > 50 mm in diameter) were reported by 3 and 6 subjects in the NIMENRIX and MENACTRA groups, respectively. Grade 3 events of swelling (i.e. > 50 mm in diameter) were reported by 3 subjects each of the two vaccine groups.

The most common solicited general symptom was fatigue with an incidence of 27.3% to 29.2% across the two vaccine groups. Headache was reported by 25.5% to 26.4% and gastrointestinal symptoms by 13.1% to 13.5% of subjects across the two vaccine groups.

Adults aged 18-55 years
In Study MenACWY-TT-035, healthy adults aged 18 through 55 years of age were administered either 1 dose of NIMENRIX, 1 dose of a licensed ACWY-PS (polysaccharide) vaccine, or 1 dose of NIMENRIX co-administered with a licensed influenza vaccine, FLUARIX®.

Table 4 includes the percentage of subjects (aged 18 through 55 years of age) with solicited adverse reactions during the 4-day post vaccination period in the NIMENRIX, ACWY-PS and Co-administered groups.

Pain was the most frequently reported solicited local symptom in each group (19.4% in the NIMENRIX group, 21.9% in the Co-administered group and 13.5% in the ACWY-PS group). Headache was the most frequently reported solicited general symptom in each group (16.3% in the NIMENRIX group, 14.2% in the ACWY-PS group, and 13.3% in the Co-administered group).

Table 4 Percentage of subjects with solicited local and general symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort), subjects 6 through 55 years of age

		MenACWY-TT-081		MenACWY-TT-071		MenACWY-TT- 035		
Age		**6-10 Years old**		**10-25 Years old**		**18-55 Years old**		
	Type	**NIMENRIX N=148**	**MenC N=50**	**NIMENRIX N=329**	**MENACTRA N=325**	**NIMENRIX N=927**	**NIMENRIX + FLUARIX N=105**	**ACWY-PS N=310**
Local Symptoms, %								
Pain	All	43.9	54.0	51.4	55.4	19.4	21.9	13.5
	Grade 3	2.0	6.0	2.4	0.6	0.4	1.0	0.3
Redness	All	39.2	38.0	25.8	20.3	8.8	5.7	4.5
	>50 mm	6.1	10.0	0.9	1.8	1.3	0.0	0.0
Swelling	All	29.7	30.0	19.1	13.5	7.9	1.0	1.9
	>50 mm	2.7	6.0	0.9	0.9	1.1	0.0	0.0
General Symptoms, %								
	Type	**NIMENRIX N=148**	**MenC N=50**	**NIMENRIX N=329**	**MENACTRA N=326**	**NIMENRIX N=927**	**NIMENRIX + FLUARIX N=105**	**ACWY-PS N=310**
Fatigue	All	22.3	22.0	29.2	27.3	12.3	9.5	9.7
	Grade 3	2.7	0.0	2.7	1.5	0.9	0.0	0.0
Fever	All ($\geq$37.5°C)	6.8	2.0	5.2	4.9	4.0	2.9	4.5
	>39.5°C	0.0	0.0	0.3	0.0	0.2	0.0	0.6
Gastro-intestinal	All	14.9	8.0	13.1	13.5	4.6	1.9	3.2
	Grade 3	0.7	0.0	1.2	1.2	0.2	0.0	0.3
Headache	All	20.3	8.0	26.1	25.5	16.3	13.3	14.2
	Grade 3	1.4	0.0	1.5	1.8	1.5	0.0	1.6

N= number of subjects with the dose documented
%= percentage of subjects reporting the symptom at least once
Study 081 and Study 071: Fever ($\geq$37.5°C) (Orally)
Study 035: Fever ($\geq$37.5°C) (Axillary)

Adults aged > 55 years

In a descriptive study a single dose of NIMENRIX was administered to 274 individuals aged 56 years and older. The adverse reactions reported in this study were already observed in younger age groups.

Common and Uncommon Clinical Trial Adverse Drug Reactions:

Additional adverse reactions reported during clinical studies included in the safety pooled analysis:

Common ($\geq$ 1% to < 10%)*: Injection site hematoma, gastrointestinal symptoms (including diarrhea, vomiting and nausea)

Uncommon ($\geq$ 0.1% to < 1%)**: insomnia, crying, hypoesthesia, dizziness, pruritus, rash, myalgia, pain in extremity, malaise, and injection site reaction (including induration, pruritus, warmth, anesthesia).

* Nausea and injection site hematoma occurred at a frequency of Uncommon in infants.
** Rash occurred at a frequency of Common in infants. The adverse reactions hypoesthesia, dizziness, pruritus, myalgia and pain in extremity were not reported in the infant clinical study.

Post-Market Adverse Drug Reactions

General disorders and administration site conditions

Unknown: extensive limb swelling at the injection site, frequently associated with erythema, sometimes involving the adjacent joint or swelling of the entire injected limb.

DRUG INTERACTIONS

Drug Interactions

In infants, NIMENRIX can be given concomitantly with combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus and Haemophilus influenzae type B vaccines, as well as 10-valent pneumococcal conjugate vaccine (PCV10).

From age 1 year and above, NIMENRIX can be given concomitantly with any of the following vaccines: hepatitis A and hepatitis B vaccines (HAV and HBV), measles-mumps-rubella vaccine (MMR), measles-mumps-rubella-varicella vaccine (MMRV), 10-valent pneumococcal conjugate vaccine or unadjuvanted seasonal influenza vaccine.

NIMENRIX can also be given concomitantly with combined diphtheria-tetanus-acellular pertussis vaccines, including combination DTaP vaccines with hepatitis B, inactivated poliovirus or *Haemophilus influenzae* type b, such as DTaP-HBV-IPV/Hib vaccine, and 13-valent pneumococcal conjugate vaccine (PCV13) in the second year of life.

Safety and immunogenicity of NIMENRIX was evaluated when sequentially administered or co-administered with a DTaP-HBV-IPV/Hib vaccine in the second year of life. The administration of NIMENRIX one month after the DTaP-HBV-IPV/Hib vaccine resulted in lower MenA, MenC and MenW-135 rSBA Geometric Mean Titres (GMTs). Clinical relevance of this observation is unknown, since at least 99.4% of subjects (N=178) had rSBA titres ≥ 8 for each group (A, C, W-135, Y). Whenever possible, NIMENRIX and a tetanus toxoid (TT) containing vaccine, such as DTaP-HBV-IPV/Hib vaccine, should be co-administered or NIMENRIX should be administered at least one month before the TT-containing vaccine.

One month after co-administration with a 10-valent pneumococcal conjugate vaccine, lower Geometric Mean antibody Concentrations (GMCs) and opsonophagocytic assay (OPA) antibody GMTs were observed for one pneumococcal serotype (18C conjugated to tetanus toxoid carrier protein). Clinical relevance of this observation is unknown. There was no impact of co-administration on the other nine pneumococcal serotypes.

If NIMENRIX is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

Use with systemic immunosuppressive medications

As with other vaccines, it may be expected that in patients receiving immunosuppressive treatment, an adequate response may not be elicited.

DOSAGE AND ADMINISTRATION

Dosing Considerations
NIMENRIX should be used in accordance with available official recommendations.

Recommended Dose and Dosage Adjustment

1. Infants From 6 to 12 Weeks of Age

Two-dose primary series
The recommended immunization series consists of 2 doses (0.5 mL each) given 2 months apart. The doses should be given at 2 and 4 months of age, followed by a booster dose at 12 months of age. The first dose may be given as early as 6 weeks of age (see CLINICAL TRIALS – Immunogenicity: Immunogenicity in infants).

2. Individuals From 12 Months of Age

A single 0.5 mL dose should be administered.

NIMENRIX may be given as a booster dose to individuals who have previously received primary vaccination with NIMENRIX or other conjugated or plain polysaccharide meningococcal vaccines (see WARNINGS AND PRECAUTIONS – Protection Against Meningococcal Disease: Persistence of serum bactericidal antibody titres and CLINICAL TRIALS – Immunogenicity: Immunogenicity in toddlers aged 12-23 months).

A second dose of NIMENRIX may be considered appropriate for some individuals (see WARNINGS AND PRECAUTIONS – Protection Against Meningococcal Disease: Persistence of serum bactericidal antibody titres).

Administration
NIMENRIX is for intramuscular injection only.

The injection sites are the anterolateral aspect of the thigh in infants, or the anterolateral aspect of the thigh or deltoid muscle in individuals from 12 months of age (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

For instructions on reconstitution of the vaccine before administration, see SPECIAL HANDLING INSTRUCTIONS.

The reconstituted vaccine is a clear colourless solution.

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

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

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Anti-capsular meningococcal antibodies protect against meningococcal diseases via complement mediated bactericidal killing. NIMENRIX induces the production of bactericidal antibodies against capsular polysaccharides of serogroups A, C, W-135 and Y when measured by assays using either rabbit complement (rSBA) or human complement (hSBA). By conjugating capsular polysaccharide to a protein carrier that contains T-cell epitopes, meningococcal conjugate vaccines like NIMENRIX change the nature of immune response to capsular polysaccharide from T-cell independent to T-cell dependent.

Canadian epidemiological data is available on the Public Health Agency of Canada website: http://www.phac-aspc.gc.ca/im/vpd-mev/meningococcal-eng.php.

STORAGE AND STABILITY

Store in a refrigerator (2°C – 8°C). The diluent may also be stored at ambient temperature (25°C).

Do not freeze. Protect from light.

For shelf-life after reconstitution of the vaccine, see SPECIAL HANDLING INSTRUCTIONS.

SPECIAL HANDLING INSTRUCTIONS

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

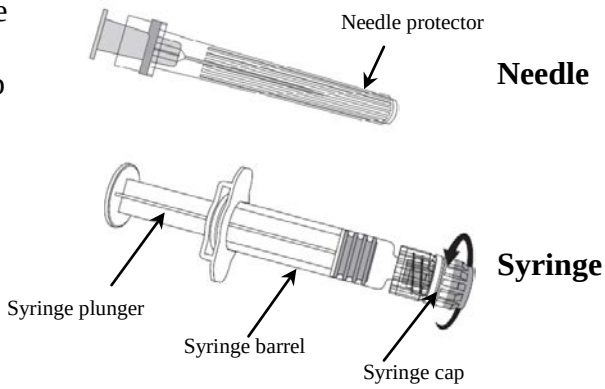
Instructions for reconstitution of the vaccine with the diluent presented in pre-filled syringe

NIMENRIX must be reconstituted by adding the entire content of the pre-filled syringe of diluent to the vial containing the powder.

To attach the needle to the syringe, refer to the below drawing.

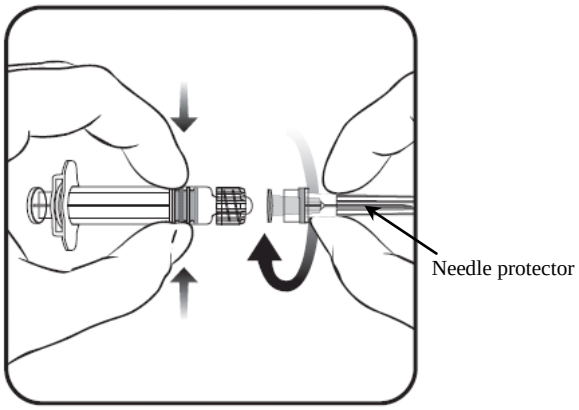
Note: However, the syringe provided with NIMENRIX might be slightly different (without screw thread) than the syringe described in the drawing. In that case, the needle should be attached without screwing.

1. Holding the syringe **barrel** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.



2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock (see drawing).

3. Remove the needle protector, which on occasion can be a little stiff.



4. Add the diluent to the powder. After the addition of the diluent to the powder, the mixture should be well shaken until the powder is completely dissolved in the diluent.

After reconstitution, the vaccine should be used promptly. Although delay is not recommended, stability has been demonstrated for 8 hours at 30°C after reconstitution. If not used within 8 hours, do not administer the vaccine.

A new needle should be used to administer the vaccine.

Instructions for reconstitution of the vaccine with diluent presented in ampoules

NIMENRIX must be reconstituted by adding the entire content of the ampoule of diluent to the vial containing the powder.

To do so, break the top of the ampoule, draw up the diluent with a syringe and add the diluent to the powder.

The mixture should be well shaken until the powder is completely dissolved in the diluent.

After reconstitution, the vaccine should be used promptly. Although delay is not recommended, stability has been demonstrated for 8 hours at 30°C after reconstitution. If not used within 8 hours, do not administer the vaccine.

A new needle should be used to administer the vaccine.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form

NIMENRIX (meningococcal polysaccharide groups A, C, W-135 and Y conjugate vaccine) is supplied as a sterile lyophilized white powder or cake in a single dose vial.

The diluent (sodium chloride and water for injections) is a sterile clear and colourless liquid supplied separately in a prefilled syringe or ampoule*.

**Format not available in Canada.*

After reconstitution, NIMENRIX is a clear colourless solution.

Composition

After reconstitution, 1 dose (0.5 mL) contains:

Active Ingredients

Neisseria meningitidis serogroup A polysaccharide[1]	*5 micrograms*
Neisseria meningitidis serogroup C polysaccharide[1]	*5 micrograms*
Neisseria meningitidis serogroup W-135 polysaccharide[1]	*5 micrograms*
Neisseria meningitidis serogroup Y polysaccharide[1]	*5 micrograms*
[1]conjugated to tetanus toxoid carrier protein	44 micrograms

Excipients

Powder:

Sucrose	28 mg
Trometamol	97 mcg

Diluent:

Sodium chloride	4.5 mg
Water for Injections	q.s. to 0.5 mL

Packaging

NIMENRIX is supplied in a 3 mL single dose glass vial. The diluent (0.5 mL) is supplied in a prefilled syringe or ampoule*.

The vials, syringes, and ampoules* are made of neutral glass Type 1.

NIMENRIX is available in pack sizes as follows:

- Single dose vial packaged with pre-filled syringe of diluent with or without needles in pack sizes of 1 and 10.
- Single dose vial packaged with ampoule* of diluent in pack sizes of 1, 10 or 100.

**Format not available in Canada.*

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

NIMENRIX is composed of the purified capsular polysaccharides of *Neisseria meningitidis* serogroups A, C, W-135 and Y, each conjugated to tetanus toxoid.

CLINICAL TRIALS

The immunogenicity of one dose of NIMENRIX has been evaluated in more than 9,000 subjects aged ≥12 months, and in approximately 1,000 subjects below 12 months of age.

In 5 clinical trials, the use of NIMENRIX as a booster following primary vaccination with NIMENRIX or other meningococcal vaccines (quadrivalent meningococcal A, C, W-135, and Y-diphtheria toxoid [DT] conjugate vaccine or monovalent MenC conjugate vaccines) was evaluated. A robust Nimenrix booster response was observed for all groups in all age ranges assessed.

Vaccine efficacy was inferred from the demonstration of immunologic non-inferiority (based mainly on comparing proportions with rabbit complement serum bactericidal assay (rSBA) titres at least 1:8) to licensed meningococcal vaccines. Immunogenicity was measured by using rSBA or human complement serum bactericidal assay (hSBA) which are biomarkers for protective efficacy against meningococcal serogroups A, C, W-135 and Y.

Table 5 Study demographics and trial design

Study #	Study Objectives	Trial design	No. of study subjects[§]	Mean age (Range)	Gender Male/ Female
6 weeks-12 months					
Men ACWY-TT -083	Immunogenicity and safety compared to MenC-CRM and MenC-TT when co-administered with PCV10 and DTaP-HBV-IPV/Hib	Open, randomized, controlled, multi-centre	Total=1841 NIMENRIX: 2 doses=458 3 doses=465 MenC-CRM=459 MenC-TT=459	8.7 weeks (6-12 weeks)	929/912
12-23 months					
Men ACWY-TT -039	Immunogenicity and safety compared to MenC-CRM vaccine and concomitant administration with measles-mumps-rubella-varicella vaccine (MMRV)	Open, randomized, controlled, multi-centre	Total=972 NIMENRIX=366 Co-admin=361 MMRV=121 MenC-CRM=124	14.6 months (12-19 months)	507/465
Men ACWY-TT -104	Immunogenicity, persistence and safety of 1 and 2 doses and concomitant administration with PCV13	Open, randomized, controlled, multi-centre	Total=802* NIMENRIX: 1 dose=203* 2 dose=197* Co-Admin=201* PCV13=201*	12.8 months (11-15 months)	427/375
2-10 years					
Men ACWY-TT -081	Immunogenicity and safety compared to MenC-CRM	Open, randomized, controlled, multi-centre	Total=395 NIMENRIX=296 MenC-CRM =99	5.6 years (2-10 years)	191/204
10-55 years					
Men ACWY-TT -035	Lot-to-lot consistency; immunogenicity and safety compared to ACWY-PS and concomitant administration with influenza virus vaccine	Partially double-blinded, randomized, controlled, multi-centre	Total=1284 NIMENRIX=885 ACWY-PS=294 Co-admin=105	35.5 years (18-55 years)	710/574
Men ACWY-TT -071	Immunogenicity and safety compared to quadrivalent meningococcal diphtheria toxoid conjugate vaccine (MENACTRA)	Observer-blinded, randomized, controlled, multi-centre	Total =951 NIMENRIX=637 MENACTRA=314	16.3 years (10-25 years)	464/487
> 55 years					
Men ACWY-TT-085	Immunogenicity, safety, and reactogenicity compared to ACWY-PS	Open, randomized, controlled	Total = 260 NIMENRIX= 194 ACWY-PS= 66	63.9 years (56-103 years)	178/82

[§]Number of subjects in according-to-protocol (ATP) cohort for immunogenicity or persistence

*Number of subjects in total vaccinated cohort

Study results

Immunogenicity

Immunogenicity in infants

In the clinical study in infants (MenACWY-TT-083), the immunogenicity of a 2-dose primary vaccination schedule (2 and 4 months of age) was evaluated (Table 6). The first dose was administered as early as 6 weeks of age. Routinely used infant vaccines DTaP-HBV-IPV/Hib and a 10-valent pneumococcal vaccine were co-administered. For group C, the immune response elicited by NIMENRIX was compared to a 2-dose priming with licensed monovalent meningococcal conjugate group C vaccines, C-CRM_{197} conjugate (MenC-CRM) and C-TT conjugate (MenC-TT) vaccines. NIMENRIX elicited a bactericidal antibody response against the four groups. The response against group C was non-inferior to the one elicited by the licensed MenC-CRM and MenC-TT vaccines in term of rSBA titres ≥8.

Booster vaccination after priming in infancy:

For subjects primed in infancy with NIMENRIX at 2 and 4 months of age and receiving a NIMENRIX booster dose at 12 months of age, the increase in rSBA and hSBA titres one month post-booster dose ranged between 15 and 80-fold for all groups (Study MenACWY-TT-083) and more than 99.0% of all infants achieved post-booster titres above 8 for both assays (Table 6).

Table 6: Study MenACWY-TT-083: Bactericidal antibody responses in infants after priming and after a booster dose

Group	Response to	Time-point*	2-dose priming rSBA**			2-dose priming hSBA***		
			N	≥8 (95% CI)	GMT (95% CI)	N	≥8 (95% CI)	GMT (95% CI)
A	NIMENRIX	Post dose 2	456	97.4% (95.4; 98.6)	203 (182; 227)	202	96.5% (93.0; 98.6)	157 (131; 188)
		Post booster	462	99.6% (98.4; 99.9)	1561 (1412.3; 1725.3)	214	99.5% (97.4;100)	1007.2 (835.7;1213.8)
C	NIMENRIX	Post dose 2	456	98.7% (97.2; 99.5)	612 (540; 693)	218	98.6% (96.0; 99.7)	1308 (1052; 1627)
		Post booster	463	99.8% (98.8; 100)	1177 (1059.1; 1308)	221	99.5% (97.5; 100)	4992.3 (4085.7; 6100)
	MenC-CRM vaccine	Post dose 2	455	99.6% (98.4; 99.9)	958 (850; 1079)	202	100% (98.2; 100)	3188 (2646; 3841)
		Post booster	446	98.4% (96.8; 99.4)	1051.4 (919.6; 1201.1)	216	100% (98.3; 100)	5438.2 (4412.4; 6702.3)
	MenC-TT vaccine	Post dose 2	457	100% (99.2; 100)	1188 (1080; 1307)	226	100% (98.4; 100)	2626 (2219; 3109)
		Post booster	459	100% (99.2; 100)	1960.2 (1776.4; 2163.1)	219	100% (98.3; 100)	5542.3 (4765.2; 6446.2)
W	NIMENRIX	Post dose 2	455	99.1% (97.8; 99.8)	1605 (1383; 1862)	217	100% (98.3; 100)	753 (644; 882)
		Post booster	462	99.8% (98.8; 100)	2777.2 (2485.1; 3103.6)	218	100% (98.3; 100)	5122.7 (4504.2; 5826.1)
Y	NIMENRIX	Post dose 2	456	98.2% (96.6; 99.2)	483 (419; 558)	214	97.7% (94.6; 99.2)	328 (276; 390)
		Post booster	462	99.4% (99.1; 99.9)	881.3 (787.5; 986.4)	217	100% (98.3; 100)	2954 (2497.9; 3493.3)

The analysis of immunogenicity was conducted on the primary according-to-protocol (ATP) cohort for immunogenicity.
*Blood sampling performed 1 month post last priming vaccination (dose 2) and 1 month post-booster.
**rSBA testing performed at Public Health England (PHE) laboratories in UK
***hSBA tested at GSK laboratories

Immunogenicity in toddlers aged 12-23 months

In the clinical study MenACWY-TT-039, the immune response to vaccination with either NIMENRIX or a licensed meningococcal C-CRM_{197} conjugate (MenC-CRM) vaccine was evaluated.

A single dose of NIMENRIX elicited rSBA responses against the four meningococcal serogroups, with a response against serogroup C that was comparable to the one elicited by the licensed MenC-CRM vaccine in term of percentages with rSBA titres ≥8 (Table 7)

Table 7 Study MenACWY-TT-039: Percentage of subjects with rSBA$^{\beta}$ titres equal to or above the cut off value of 1:8 at day 42 post vaccination

Serogroup	N	NIMENRIX (95% CI)	N	Active Control (MenC-CRM)	Difference in percentage (ACWY-TT minus MenC-CRM)* (95%CI)
rSBA-Men A	354	99.7% (98.4; 100)	-	-	-
rSBA-Men C	354	99.7% (98.4; 100)	121	97.5% (92.9; 99.5)	2.20 (0.29; 6.78)
rSBA-MenW-135	354	100% (99.0; 100)	-	-	-
rSBA-Men Y	354	100% (99.0; 100)	-	-	-

N = number of subjects with results available
% = percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
ATP cohort for immunogenicity
*LL of 95% CI is above non-inferiority limit of -10%.
$^{\beta}$tested at GSK Laboratories

The Geometric Mean Titres (GMTs) for MenC 42 days after vaccination were higher in children who received NIMENRIX than those who received MenC-CRM (478 vs. 212). GMTs ranged between 2205 and 2729 for serogroups A, W-135 and Y in the NIMENRIX group.

In addition this study evaluated the immunogenicity for hSBA prior to and 42 days after the first vaccine dose with NIMENRIX or the control vaccine (MenC-CRM). At 42 days after vaccination, 98.5% of the subjects in the NIMENRIX group and 81.9% of subjects in the MenC-CRM group had hSBA-MenC titres ≥ 8. In the NIMENRIX group the percentage of subjects with hSBA titres ≥ 8 ranged between 77.2% and 87.5 % for serogroups A, W-135 and Y.

In Study Men ACWY-TT-104, the immune response following one or two doses of NIMENRIX given 2 months apart was evaluated one month after the last vaccination. NIMENRIX elicited bactericidal responses against all four groups that were similar in terms of % with rSBA titre ≥8 and GMT after one or two doses (Table 8).

Table 8: Study MenACWY-TT-104: Bactericidal antibody responses (rSBA*) in toddlers aged 12-14 months

Group	Response to	Timing	Study MenACWY-TT-104 rSBA[1]		
			N	≥8 (95%CI)	GMT (95% CI)
A	NIMENRIX 1 dose	Post dose 1	180	97.8 (94.4, 99.4)	1437 (1118.3, 1846.6)
	NIMENRIX 2 doses	Post dose 1	158	96.8 (92.8, 99.0)	1275.2 (970.5, 1675.4)
		Post dose 2	150	98.0 (94.3, 99.6)	1176.3 (921.8, 1501)
C	NIMENRIX 1 dose	Post dose 1	179	95.0 (90.7, 97.7)	452.3 (345.6, 591.9)
	NIMENRIX 2 doses	Post dose 1	157	95.5 (91.0, 98.2)	369.3 (280.9, 485.5)
		Post dose 2	150	98.7 (95.3, 99.8)	639.1 (521.8, 782.9)
W-135	NIMENRIX 1 dose	Post dose 1	180	95.0 (90.8, 97.7)	2120.2 (1601.0, 2807.8)
	NIMENRIX 2 doses	Post dose 1	158	94.9 (90.3, 97.8)	2030.1 (1510.7, 2728.2)
		Post dose 2	150	100 (97.6, 100)	3533 (2914.5, 4282.7)
Y	NIMENRIX 1 dose	Post dose 1	180	92.8 (88.0, 96.1)	951.8 (705.0, 1284.9)
	NIMENRIX 2 doses	Post dose 1	157	93.6 (88.6, 96.9)	933.3 (692.3, 1258.3)
		Post dose 2	150	99.3 (96.3, 100)	1133.6 (944.5, 1360.5)

The analysis of immunogenicity was conducted on the according-to-protocol (ATP) cohort for immunogenicity
[1] blood sampling performed 21-48 days post vaccination
*tested at Public Health England laboratories

In Study MenACWY-TT-104, the serum bactericidal activity was also measured using hSBA as a secondary endpoint. NIMENRIX elicited bactericidal responses against groups W-135 and Y that were higher in terms of % with hSBA titre ≥8 when two doses were given compared with one. Similar responses in terms of % with hSBA titre ≥8 were observed with groups A and C (Table 9).

Table 9: Study MenACWY-TT-104: Bactericidal antibody responses (hSBA*) in toddlers aged 12-14 months

Group	Response to	Timing	Study MenACWY-TT-104 hSBA[1]		
			N	≥8 (95%CI)	GMT (95% CI)
A	NIMENRIX 1 dose	Post dose 1	74	95.9 (88.6, 99.2)	118.0 (86.8, 160.5)
	NIMENRIX 2 doses	Post dose 1	66	97.0 (89.5, 99.6)	132.9 (98.1, 180.1)
		Post dose 2	66	97.0 (89.5, 99.6)	170.5 (126.2, 230.2)
C	NIMENRIX 1 dose	Post dose 1	78	98.7 (93.1, 100)	151.9 (104.8, 220.4)
	NIMENRIX 2 doses	Post dose 1	70	95.7 (88.0, 99.1)	161 (110, 236)
		Post dose 2	69	100 (94.8, 100)	1753.3 (1277.7, 2404.2)
W-135	NIMENRIX 1 dose	Post dose 1	72	62.5 (50.3, 73.6)	27.5 (16.1, 46.8)
	NIMENRIX 2 doses	Post dose 1	61	68.9 (55.7, 80.1)	26.2 (16.0, 43.0)
		Post dose 2	70	97.1 (90.1, 99.7)	756.8 (550.1, 1041.3)
Y	NIMENRIX 1 dose	Post dose 1	71	67.6 (55.5, 78.20)	41.2 (23.7, 71.5)
	NIMENRIX 2 doses	Post dose 1	56	64.3 (50.4, 76.6)	31.9 (17.6, 57.9)
		Post dose 2	64	95.3 (86.9, 99.0)	513.0 (339.4, 775.4)

The analysis of immunogenicity was conducted on the according-to-protocol (ATP) cohort for immunogenicity
(1) blood sampling performed 21-48 days post vaccination
*tested at GSK laboratories

Immunogenicity in children aged 2 to 10 years

In study (MenACWY-TT-081) conducted in subjects aged 2-10 years, one group of subjects received a dose of NIMENRIX and a second group a dose of a licensed MenC-CRM vaccine as a comparator.

Table 10 Study MenACWY-TT-081: Percentage of subjects with a vaccine response in terms of rSBA* antibodies one month following vaccination

Serogroup	N	NIMENRIX % (95% CI)	N	Active Control (MenC-CRM) % (95% CI)	Difference in vaccine response rate (ACWY-TT minus MenC-CRM) (95%CI)*
rSBA-Men A	226	94.7% (90.9; 97.2)	-	-	-
rSBA-Men C	268	94.8% (91.4; 97.1)	92	95.7% (89.2; 98.8)	-0.88 (**-5,25**; 5,57)
rSBA-MenW-135	282	98.6% (96.4; 99.6)	-	-	-
rSBA-Men Y	285	96.5% (93.6; 98.3)	-	-	-

Vaccine response defined as:
For initially seronegative subjects: post-vaccination antibody titre ≥ 1:32 at one month post-vaccination
For initially seropositive subjects: antibody titre at one month post-vaccination ≥ 4 fold the pre-vaccination antibody titre
N = number of subjects with pre- and post-vaccination results available
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit
Bold: LL of 95% CI is above non-inferiority limit of -10% for MenC.
*tested at GSK Laboratories

The non-inferiority of the NIMENRIX vaccine compared to the MenC-CRM vaccine in terms of serum bactericidal antibody vaccine response to rSBA-MenC, one month after vaccination was demonstrated since the lower limit of the 95% CIs on the difference between the NIMENRIX and (minus) the MenC-CRM group was -5.25%, which was above the pre-specified non-inferiority limit of -10%.

The GMT elicited by MenC-CRM was higher than the one observed for the NIMENRIX vaccine (5291.6 vs. 2794.8). The percentage of subjects with rSBA-MenC titre ≥ 128 was similar for both vaccines (100% vs. 99.3%). For NIMENRIX GMTs ranged between 6236.1 and 8549.5 for rSBA MenA, W-135 and Y.

Immunogenicity in adolescents/adults aged 10-25 years and adults aged 18 up to 55 years
In a Phase II head-to-head study conducted in Canada and the US with NIMENRIX and the licensed quadrivalent meningococcal diphtheria toxoid conjugate vaccine (ACWY-DT) MENACTRA in subjects aged 10-25 years (study Men ACWY-TT-071), either one dose of NIMENRIX or one dose of MENACTRA was administered.

NIMENRIX was demonstrated to be immunologically non-inferior to MENACTRA in terms of the percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY vaccine response one month after vaccination (all the lower limits of the two-sided 95% CI for the difference between groups were greater than or equal to -10%) (Table 11).

The GMT elicited by NIMENRIX ranged from 49.6 to 755.8 for hSBA MenA, C, W-135 and Y and the GMT elicited by MENACTRA ranged from 41.3 to 543.4 for hSBA MenA, C, W-135 and Y.

Table 11 Study Men ACWY-TT-071: Percentage of subjects with vaccine response to hSBA* antibodies one month following vaccination

Serogroup	N	NIMENRIX % (95% CI)	N	MENACTRA % (95% CI)	Difference in vaccine response rate (ACWY-TT Lot A minus ACWY-DT)* (95%CI)
hSBA-Men A	310	70.3% (64.9; 75.4)	297	64.3% (58.6; 69.8)	6.01 (**-1.45**: 13.44)
hSBA-Men C	281	77.2% (71.9; 82.0)	274	76.3% (70.8; 81.2)	0.95 (**-6.10**; 8.00)
hSBA-MenW-135	279	71.0% (65.3; 76.2)	289	64.0% (58.2; 69.6)	6.95 (**-0,76**; 14.59)
hSBA-Men Y	293	51.2% (45.3; 57.1)	295	39.0% (33.4; 44.8)	12.21 (**4,17**; 20.10)

Vaccine response defined as:
For initially seronegative subjects: post-vaccination antibody titer ≥ 1:8 at one month post-vaccination
For initially seropositive subjects: antibody titer at one month post-vaccination ≥ 4-fold the pre-vaccination antibody titer
N = number of subjects with pre- and post-vaccination results available
95% CI = Standardized asymptotic 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Bold: LL of 95% CI is above non-inferiority limit of -10%.
*tested at GSK Laboratories

In another clinical study, conducted in adults 18-55 years of age (study MenACWY-TT-035), either one dose of NIMENRIX or one dose of the ACWY-PS vaccine were administered.

Table 12 Study MenACWY-TT-035: Percentage of subjects with vaccine response to rSBA* antibodies one month following vaccination

Serogroup	N	NIMENRIX % (95% CI)	N	Active Control (ACWY-PS) % (95% CI)	Difference in vaccine response rate (NIMENRIX minus ACWY-PS) (95%CI)*
rSBA-Men A	743	80.1% (77.0; 82.9)	252	69.8% (63.8; 75.4)	10.24 (**4.11**; 16.78)
rSBA-Men C	849	91.5% (89.4; 93.3)	288	92.0% (88.3; 94.9)	-0.49 (**-3.85**; 3.57)
rSBA-MenW-135	860	90.2% (88.1; 92.1)	283	85.5% (80.9; 89.4)	4.72) (**0.49**; 9.65)
rSBA-Men Y	862	87.0% (84.6; 89.2)	288	78.8% (73.6; 83.4)	8.19 (**3.24**; 13.69)

Vaccine response defined as:
For initially seronegative subjects: post-vaccination antibody titre ≥ 1:32 at one month post-vaccination
For initially seropositive subjects: antibody titre at one month post-vaccination ≥ 4 fold the pre-vaccination antibody titre
N = number of subjects with pre- and post-vaccination results available
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit
Bold: LL of 95% CI is above non-inferiority limit of -10%
*tested at GSK Laboratories

The response to the four meningococcal groups elicited by NIMENRIX was either similar or higher than the one elicited by the ACWY-PS vaccine. In adults, NIMENRIX was demonstrated to be immunologically non-inferior to the ACWY-PS vaccine. NIMENRIX induced higher GMTs and vaccine response for serogroups A, W-135 and Y than the ACWY-PS vaccine.

The GMT elicited by NIMENRIX ranged from 3624.7 to 8865.9 for rSBA MenA, C, W-135 and Y and the GMT elicited by MENACTRA ranged from 2127.2 to 7371.2 for rSBA MenA, C, W-135 and Y.

Immunogenicity in adults aged > 55 years

A descriptive study (MenACWY-TT-085) was conducted to evaluate the immunogenicity of NIMENRIX compared to ACWY-PS vaccine, in terms of Meningococcal serogroups A, C, W-135 and Y bactericidal vaccine response[a] one month after the vaccination. A single dose of vaccine was administered to 369 Lebanese adults 56 years of age and older (including 274 and 95 subjects in the treatment and control groups, respectively). The analysis of immunogenicity was evaluated based on 260 subjects included in the ATP cohort for immunogenicity (194 and 66 subjects in the treatment and control groups, respectively). The vaccine response ranged from 76.6% (rSBA-MenA) to 81.9% (rSBA-MenY) in the NIMENRIX group and from 84.8% (rSBA-MenC) to 91.7% (rSBA-MenA) in the ACWY-PS group. Of the 194 subjects in the treatment group, the percentage of subjects with rSBA titres ≥ 128 before vaccination ranged from 45% (MenC) to 62% (MenY). Overall, at one month post-vaccination the percentage of vaccinees with rSBA titres ≥ 128 ranged from 93% (MenC) to 97% (MenY). The supplementary analysis showed that in the subgroup aged > 65 years the percentage of vaccinees with rSBA titres ≥ 128 at one month post-vaccination ranged from 90% (MenA) to 97% (MenY).

Persistence of immune response

The persistence of the immune response elicited by NIMENRIX was evaluated up to 60 months after vaccination in subjects aged 12 months to 55 years.

For all serogroups (A, C, W-135, Y), the persistence of the antibodies elicited by NIMENRIX was similar or higher than those induced by the licensed meningococcal vaccines [i.e. MenC-CRM vaccine in subjects aged 12-23 months, and ACWY-PS vaccine in subjects older than 2 years of age, and MENACTRA in subjects aged 11-25 years].

Persistence of immune response in toddlers aged 12-23 months

In study MenACWY-TT-048, the persistence of the immune response was evaluated by rSBA and hSBA up to four years in toddlers in terms of percentage of subjects with antibody titres ≥ 1:8 for each of the 4 serogroups in toddlers primed in study MenACWY TT 039.

Forty-eight months following primary vaccination, 27% of the children were included in this evaluation (Table 13).

[a]Vaccine response to meningococcal antigens (MenA, MenC, MenW-135 and MenY) at one month post vaccination, defined as:

- for initially seronegative subjects (rSBA titre less than 1:8), post vaccination rSBA titre ≥ 1:32
- for initially seropositive subjects with rSBA titre between 1:8 and 1:128, at least four-fold increase in rSBA titre from pre to post vaccination
- for initially seropositive subjects with rSBA titres ≥ 1:128, at least two-fold increase in rSBA titre from pre to post vaccination

Table 13 4 years persistence data in toddlers aged 12-23 months at vaccination (Study MenACWY-TT-048)

Serogroup	Group	Time-point (Year)	rSBA*		hSBA**	
			N	% Response	N	% Response
A	**NIMENRIX**	3	262	59.9%	251	35.9%
		4	224	74.1%	198	28.8%
C	**NIMENRIX**	3	262	35.9%	253	78.3%
		4	225	40.4%	209	73.2%
	MenC-CRM vaccine	3	46	13.0%	31	41.9%
		4	45	35.6%	32	46.9%
W-135	**NIMENRIX**	3	261	49.8%	254	82.3%
		4	225	49.3%	165	80.6%
Y	**NIMENRIX**	3	262	53.8%	250	72.0%
		4	225	58.2%	130	65.4%

The analysis of immunogenicity was conducted on ATP cohort for persistence adapted for each time-point.
*rSBA testing performed at Public Health England (PHE) laboratories in UK
** tested at GSK laboratories
Vaccine response defined as: post-vaccination antibody titre ≥ 1:8

In study MenACWY-TT-032, the persistence of the immune response was evaluated by rSBA and hSBA in toddlers aged 12-23 months up to 5 years. At year 5, for all four serogroups W-135, Y, A and C, 34.7%, 42.9%, 73.5% and 77.6% of subjects in the NIMENRIX group had rSBA titres ≥ 1:8, respectively. In the MenC-CRM group, 63.6% of subjects had rSBA MenC titres ≥ 1:8 for serogroup C. For serogroups C, W-135 and Y, at least 80.0% of subjects in the NIMENRIX group had hSBA titres ≥ 1:8; for serogroup A this was only 35.6%. In the MenC-CRM group, 90.9% of subjects had hSBA-MenC titres ≥ 1:8.

Persistence of immune response in children aged 2-10 years

In study MenACWY-TT-088 (Table 14), the persistence of the immune response was evaluated by rSBA and hSBA up to 68 months after vaccination in children 2-10 years of age primed in study MenACWY-TT-081 (Table 10).

Table 14 68 months persistence data in children aged 2-10 years at vaccination (Study MenACWY-TT-088)

Serogroup	Group	Time-point (months)	rSBA*		hSBA**	
			N	% response	N***	% response
A	**NIMENRIX**	32	193	86.5%	90	25.6%
		44	189	85.7%	89	25.8%
		68	178	86.5%	170	40.6%
C	**NIMENRIX**	32	192	64.6%	90	95.6%
		44	189	37.0%	82	76.8%
		68	178	39.9%	172	75.6%
	MenC-CRM vaccine	32	69	76.8%	33	90.9%
		44	66	45.5%	31	64.5%
		68	61	62.3%	57	75.4%
W-135	**NIMENRIX**	32	193	77.2%	86	84.9%
		44	189	68.3%	87	80.5%
		68	178	52.8%	159	78.6%
Y	**NIMENRIX**	32	193	81.3%	91	81.3%
		44	189	62.4%	76	82.9%
		68	178	71.3%	159	73.0%

The analysis of immunogenicity was conducted on ATP cohort for persistence adapted for each time-point.
*rSBA testing performed at PHE laboratories in UK
** tested at GSK laboratories
***at month 32, a subset of subjects were tested for hSBA
Vaccine response defined as: post-vaccination antibody titre ≥ 1:8

Persistence of immune response vs. MENACTRA in adolescents and adults aged 11-25 years evaluated by hSBA

In study MenACWY-TT-059, the persistence of the immune response was evaluated by hSBA up to 5 years after vaccination compared to MENACTRA in adolescents and adults 11-25 years of age primed in study MenACWY-TT-052 (Table 15). At 1, 3 and 5 years following the primary vaccination 64% / 60%, 58% / 43.2%, and 25% / 23% of the subjects were included in the evaluation for NIMENRIX / MENACTRA, respectively.

For all groups (A, C, W-135, Y), the persistence of the antibodies elicited by NIMENRIX was similar or higher than those induced by MENACTRA.

Table 15 1 month post-vaccination and 5 years persistence data in adolescents and adults 11-25 years of age evaluated by hSBA* (Study MenACWY-TT-059)

Serogroup	Time-point	N	NIMENRIX %	N	Active Control (MENACTRA) %
hSBA-Men A	Month 1	356	82.0%	107	73.8%
	Year 1	350	29.1%	111	31.5%
	Year 3	316	37.3%	79	48.1%
	Year 5	141	48.9%	45	44.4%
hSBA-Men C	Month 1	359	96.1%	113	99.1%
	Year 1	336	94.9%	105	73.3%
	Year 3	319	93.1%	81	81.5%
	Year 5	140	92.9%	44	79.5%
hSBA-MenW-135	Month 1	334	91.0%	97	75.3%
	Year 1	327	98.5%	108	75.9%
	Year 3	323	95.4%	80	85.0%
	Year 5	138	87.0%	44	84.1%
hSBA-Men Y	Month 1	364	95.1%	111	81.1%
	Year 1	356	97.8%	112	86.6%
	Year 3	321	96.0%	80	88.8%
	Year 5	142	94.4%	44	90.9%

The analysis of immunogenicity was conducted on ATP cohort for persistence adapted for each time-point.
* tested at GSK laboratories

Vaccine response defined as: post-vaccination antibody titre ≥ 1:8

Immune memory

In study MenACWY-TT-014, the induction of immune memory was assessed one month after the administration of a fifth of the dose of ACWY-PS vaccine (10 mcg of each polysaccharide) to children in the third year of life previously primed in the study MenACWY-TT-013 with NIMENRIX or a licensed MenC-CRM vaccine at the age of 12 to 14 months.

One month after the challenge dose, the GMTs elicited by the subjects primed with NIMENRIX increased by 6.1 to 34 fold for serogroups A, C, W-135 and Y and indicate that NIMENRIX induces immune memory to serogroups A, W-135 and Y. The post-challenge rSBA-MenC GMT was similar in both study groups, indicating that NIMENRIX induces an analogous immune memory to serogroup C as the licensed MenC-CRM vaccine (Table 16).

Table 16 Immune response (rSBA*) 1 month after a challenge vaccination in subjects primed with NIMENRIX or a MenC-CRM vaccine at the age of 12 to 14 months (Study MenACWY-TT-014)

Group	Response to	Pre-challenge		Post-challenge	
		N	GMT	N	GMT
A	**NIMENRIX**	32	544	25	3322
C	**NIMENRIX**	31	174	32	5966
	MenC-CRM vaccine	28	34	30	5265
W-135	**NIMENRIX**	32	644	32	11058
Y	**NIMENRIX**	32	440	32	5737

The analysis of immunogenicity was conducted on ATP cohort for immunogenicity.
*tested at GSK Laboratories

Booster response

Nimenrix booster vaccination after priming in toddlers, children, adolescents and adults
For subjects primed with NIMENRIX aged 1 year and above and boosted with NIMENRIX 4 or 5 years later, more than 99.0% of all subjects achieved post-booster SBA titres ≥ 1:8 for both assays (Studies MenACWY-TT-062, 048, 059, 088). One month after the booster vaccination, the GMTs elicited indicate that NIMENRIX induces immune memory to groups A, C, W-135, and Y.

In study MenACWY-TT-048, a booster response was evaluated in children vaccinated 4 years earlier (at toddler age) in study MenACWY-TT-039 (Table 17). Children were primed and boosted with the same vaccine: either NIMENRIX or a MenC-CRM vaccine. A robust increase in rSBA and hSBA GMTs was observed from pre booster dose to one month post booster dose of NIMENRIX (Table 17). One year after NIMENRIX booster, SBA titres ≥ 1:8 persisted in at least 95.5% of subjects.

Table 17 Immune response (rSBA* and hSBA) pre-booster and 1 month after post-booster in subjects vaccinated either with NIMENRIX or a MenC-CRM vaccine 4 years earlier (at toddler age) (Study MenACWY-TT-048)**

Group	Response to	Time Point	rSBA*		hSBA**	
			N	GMT	N	GMT
A	**NIMENRIX**	Pre-Booster	212	112	187	5
		Post-Booster	214	7173	202	1343
C	**NIMENRIX**	Pre-Booster	213	12	200	31
		Post-Booster	215	4512	209	15831
	MenC-CRM vaccine	Pre-Booster	43	14	31	12
		Post-Booster	43	3718	33	8646
W-135	**NIMENRIX**	Pre-Booster	213	30	158	48
		Post-Booster	215	10950	192	14411

Table 17 Immune response (rSBA* and hSBA) pre-booster and 1 month after post-booster in subjects vaccinated either with NIMENRIX or a MenC-CRM vaccine 4 years earlier (at toddler age) (Study MenACWY-TT-048)**

Group	Response to	Time Point	rSBA*		hSBA**	
			N	GMT	N	GMT
Y	NIMENRIX	Pre-Booster	213	37	123	30
		Post-Booster	215	4585	173	6776

The analysis of immunogenicity was conducted on the booster ATP cohort for immunogenicity.
*rSBA testing performed at HPA laboratories in UK
**tested at GSK laboratories

When NIMENRIX was used as a booster following primary vaccination with a MenACWY-DT conjugate vaccine or a monovalent MenC conjugate vaccine (study MenACWY-TT-059, 10 to 25 years of age at primary vaccination and study MenACWY-TT-088, 2 to 10 years of age at primary vaccination), the titres increased by 48-340 fold for all groups and 100% of the subjects reached SBA titres ≥ 1:8.

Immunogenicity in subjects previously vaccinated with a plain polysaccharide meningococcal vaccine

In study MenACWY-TT-021 conducted in subjects aged 4.5-34 years, the immunogenicity of NIMENRIX administered between 30 and 42 months after vaccination with an ACWY-PS vaccine was compared to the immunogenicity of NIMENRIX administered to age-matched subjects who had not been vaccinated with any meningococcal vaccine in the preceding 10 years. An immune response (rSBA titre ≥8) was observed against all serogroups (A, C, W-135, Y) in all subjects regardless of the meningococcal vaccine history. The rSBA GMTs were significantly lower in the subjects who had received a dose of ACWY-PS vaccine 30-42 months prior to NIMENRIX. However, rSBA GMTs did increase post-vaccination for all four serogroups, ranging from 3.9- to 30.1- fold in the ACWY-PS group and from 11.8- to 246.0-fold in the no ACWY-PS group. At least 97.0% of the subjects in the ACWY-PS group demonstrated post-vaccination rSBA titres ≥ 1:128 for all four serogroups.

TOXICOLOGY

Non-clinical data reveal no special hazard for humans based on local tolerance, acute toxicity, repeated dose toxicity, developmental/reproductive toxicity and fertility studies.

Table 18 Nonclinical toxicology studies

Study type and species	Route and dosage regimen	Results
Local tolerance and acute toxicity New Zealand White rabbit	One intramuscular injection; full human dose	No distinct treatment-related changes in general and local clinical signs and body weight. No macroscopic abnormalities seen at injection site. A slight mononuclear type inflammation was observed microscopically at the injection sites of both the saline control and MenACWY-TT groups.
Repeated dose toxicity New Zealand White rabbit	Five repeated intramuscular injections two weeks apart; full human dose per injection	No treatment-related changes observed in general and in local clinical signs, ophthalmoscopy, rectal body temperature, haematology, clinical chemistry or organ weights. Very slight to slight inflammation in the injected muscles which diminished distinctly over time with a clear recovery process observed 28-days after the last dose. No adverse vaccine formulation-related histopathological changes were observed any other tissues or organs.
Reproductive and developmental toxicity Wistar rat	Intramuscular injection 42 and 28 days before mating and on gestation days 6, 8, 11 and 15; 2/5 of the full human dose per injection (200 mcL)	No treatment-related effects on maternal toxicity, prenatal development (including external, visceral and skeletal abnormalities), or postnatal development

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PART III: CONSUMER INFORMATION

NIMENRIX®
Meningococcal polysaccharide groups A, C, W-135 and Y conjugate vaccine

This leaflet is part III of a three-part "Product Monograph" published when NIMENRIX was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NIMENRIX. Contact your health professional if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is used for:
NIMENRIX is a vaccine that may be given to infants from the age of 6 weeks, children, adolescents and adults up to 55 years old to prevent illness caused by *Neisseria meningitidis* types A, C, W-135 and Y bacteria (germs).

Neisseria meningitidis types A, C, W-135 and Y bacteria most often cause meningitis (infection of the tissue lining the brain) and septicemia (infection of the blood). These diseases can be highly infectious and are sometimes fatal.

As with all vaccines, NIMENRIX may not fully protect all people who are vaccinated.

NIMENRIX will only protect against infections caused by groups of *Neisseria meningitidis* for which the vaccine has been developed.

What it does:
The vaccine works by causing the body to produce its own protection (antibodies) against these bacteria. The vaccine cannot cause these diseases.

When it should not be used:
Please see WARNINGS AND PRECAUTIONS section.

What the medicinal ingredient is:
Each 0.5 mL dose contains 5 micrograms of each of the *Neisseria meningitidis* capsular polysaccharides A, C, W-135 and Y each coupled to tetanus toxoid as a carrier protein.

What the important non-medicinal ingredients are:
NIMENRIX contains the following non-medicinal ingredients:

- Powder: sucrose, trometamol
- Diluent: sodium chloride, water for injections

What dosage forms it comes in:
NIMENRIX is presented as a powder and diluent for solution for injection.

WARNINGS AND PRECAUTIONS

NIMENRIX should not be given if you have previously had any allergic reaction to NIMENRIX, or any ingredient contained in NIMENRIX. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

BEFORE you use NIMENRIX talk to your health professional if:

- you or your child have/has a severe infection with a high temperature. In these cases, the vaccination will be postponed until recovery. A minor infection such as a cold should not be a problem, but talk to your health professional first.
- you or your child have/has a bleeding problem or bruise(s) easily.
- you or your child have/has a weakened immune system, for example due to HIV infection or complement deficiencies or due to medicines that suppress the immune system (for example, eculizumab). You or your child may not get the full benefit from NIMENRIX, or may remain at increased risk for disease caused by meningococcal groups A, C, W-135 and Y bacteria even if you develop antibodies following vaccination with Nimenrix.
- you are pregnant or breastfeeding.

Fainting can occur following, or even before, any needle injection, therefore tell your health professional if you/your child fainted with a previous injection.

INTERACTIONS WITH THIS VACCINE

Please tell your health professional if you/your child are/is taking or have/has recently taken any other medicines, including medicines obtained without a prescription or have/has recently received any other vaccine.

NIMENRIX may not work as well if you/your child are/is taking medicines that reduce the effectiveness of your/your child's immune system to fight infection.

NIMENRIX can be given at the same time as other vaccines such as hepatitis A and hepatitis B vaccines, measles-mumps-rubella vaccine, measles-mumps-rubella-varicella vaccine, 10-valent pneumococcal conjugate vaccine or unadjuvanted seasonal influenza vaccine.

In the first two years of life, NIMENRIX can also be given at the same time or at least one month before a combined diphtheria - tetanus - acellular pertussis vaccine, including combination diphtheria - tetanus - acellular pertussis vaccine with hepatitis B, inactivated poliovirus or *Haemophilus*

influenzae type b, such as DTaP-HBV-IPV/Hib vaccine, and 13-valent pneumococcal conjugate vaccine.

A different injection site will be used for each vaccine.

PROPER USE OF THIS VACCINE

Usual dose:
Your health professional will give NIMENRIX as an injection into the muscle, in the upper arm or thigh.

NIMENRIX is given as an injection of 0.5 mL.

Your doctor will tell you if and when you need an additional dose of NIMENRIX, especially if you or your child:

- received the first dose at 12-23 months of age and could be at risk of infection caused by *Neisseria meningitidis* types A, C, W-135 and Y
- were more than 2 years old when first vaccinated and could be at risk of infection caused by *Neisseria meningitidis* type A.

Infants from 6 to 12 weeks of age
Your child will receive 2 injections given 2 months apart at 2 and 4 months of age (the first injection may be given from the age of 6 weeks).

At 12 months of age, your child will receive an additional injection (booster).

You will be informed when your child should come back for their next injection. If your child misses a scheduled injection, it is important that you make another appointment. Make sure your child finishes the complete vaccination course.

From 12 months to 55 years of age
Toddlers, children, adolescents and adults should receive one dose of vaccine.

Overdose:

In case of overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

A vaccine, like any medicine, may cause serious problems, such as severe allergic reactions. The risk of NIMENRIX causing serious harm is extremely small. The small risks associated with NIMENRIX are much less than the risk associated with getting the disease.

In infants, adolescents and adults, very common side effects (in more than 1 in 10 doses of the vaccine) after having NIMENRIX are loss of appetite, irritability, drowsiness, headache, fever, swelling, pain and redness at the injection site and fatigue.

Common side effects (in more than 1 in 100 doses of the vaccine) after having NIMENRIX are gastrointestinal symptoms including diarrhoea, vomiting and nausea, and injection site hematoma.

Uncommon side effects (in more than 1 in 1,000 doses of the vaccine) after having NIMENRIX are insomnia, crying, dizziness, decreased feeling or sensitivity especially in the skin, itching, rash, aching muscles, pain in extremity (pain in the limb), generally feeling unwell, and injection site reaction (such as a hard lump at the injection site, itching warmth and loss of feeling).

The most common side effects reported during clinical trials usually lasted only one to two days and were not usually severe.

The following additional side effect has been reported rarely (in up to 1 in 1,000 doses of the vaccine): large swelling of the vaccinated limb associated with redness.

Tell your health professional as soon as possible if you or your child does not feel well after receiving NIMENRIX.

Do not be alarmed by this list of possible side effects. It is possible that you or your child will have no side effects from vaccination.

This is not a complete list of side effects. For any unexpected effects while taking NIMENRIX, contact your health professional.

HOW TO STORE IT

Keep out of reach and sight of children. Store in a refrigerator (2°C – 8°C). Do not freeze. Store in the original package in order to protect from light.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

For health care professionals:
If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in your province/territory.

For the General Public:
Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada:

By toll-free telephone: 1-866-844-0018
By toll-free fax: 1-866-844-5931
By email: caefi@phac-aspc.gc.ca
At the following website:
http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php

By regular mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road
Ottawa, Ontario
K1A 0K9 Address Locator 6502A

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at www.pfizer.ca or by contacting the sponsor,
Pfizer Canada ULC
at: 1-800-463-6001 (Medical Information)

This leaflet was prepared by Pfizer Canada ULC

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