Package Insert

MENACTRA

Meningococcal Polysaccharide vaccine, Groups A, C, Y and W-135 combined

Approved 29 July 2014

South Africa

SCHEDULING STATUS: **S4**

PROPRIETARY NAME AND DOSAGE FORM:

MENACTRA®, Solution for Injection

Descriptive name:

MENACTRA®, Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine

COMPOSITION:

Each 0,5 ml dose of the vaccine contains:

Active ingredients

- Meningococcal (Serogroup A) Polysaccharide (Monovalent Conjugate) 4,0 mcg
- Meningococcal (Serogroup C) Polysaccharide (Monovalent Conjugate) 4,0 mcg
- Meningococcal (Serogroup Y) Polysaccharide (Monovalent Conjugate) 4,0 mcg
- Meningococcal (Serogroup W-135) Polysaccharide (Monovalent Conjugate) 4,0 mcg

each of the four polysaccharides is conjugated to diphtheria toxoid

Diphtheria toxoid protein Approximately 48 mcg*

*Diphtheria Toxoid quantity is approximate and dependant on the conjugate polysaccharide to protein ratio.

There is no latex in any component of the single dose presentation.

Excipients

Sodium Chloride, Dibasic Sodium Phosphate anhydrous and Water for injection.

PHARMACOLOGICAL CLASSIFICATION:

A30.1 Antigens

PHARMACOLOGICAL ACTION:

Pharmacodynamics

Meningococcal disease including meningitis and septicaemia is caused by the bacterium *N. meningitidis* from which several serogroups have been identified. MENACTRA vaccine can provide protection against infections caused by serogroups A, C, Y and W-135.

Immunogenicity

The immunogenicity of MENACTRA vaccine has been studied in six clinical trials among adolescents and adults aged 11 through 55 years, in four clinical trials among children 2 through 10 years of age and in three clinical trials in infants 9 through 18 months of age.

MENACTRA vaccine induces the production of antibodies specific to the capsular polysaccharides of all vaccine serogroups (A, C, Y and W-135), which are capable of killing the corresponding bacteria. Immunogenicity was assessed by measuring these functional antibodies in a Serum Bactericidal Assay (SBA) using baby rabbit (SBA-BR) or human (SBA- HC) serum as the complement source.

Immunogenicity in the population 9 months through 23 months of age

The immunogenicity of MENACTRA vaccine has been studied in three clinical trials in approximately

2250 infants 9 through 18 months of age where one or two doses were administered either alone or with concomitant paediatric vaccine(s) (MMRV or PCV). A subset of the participants in these trials received MENACTRA vaccine concomitantly with MMRV + Hib vaccine.

In a primary study, the majority of the participants in groups that received the second dose of MENACTRA vaccine alone or with concomitant paediatric vaccine(s) achieved SBA-HC titers ≥ 1:8 for all serogroups. Groups that received the second dose of MENACTRA vaccine alone had

≥ 91% of subjects achieving an SBA-HC titer ≥ 1:8 for serogroups A, C, and Y, and ≥ 86 % for serogroup W -135. When the second dose of MENACTRA vaccine was given concomitantly with MMRV (or MMRV + Hib) or with PCV, the percentages of subjects with SBA-HC titers ≥ 1:8 were high (> 90 % for serogroups A, C and Y, and > 81 % for serogroup W-135). SBA-HC GMTs were high for all serogroups.

Administration of MENACTRA vaccine to toddlers at 12 months and 15 months of age (N = 65) as evaluated in a US study. Prior to the first dose, 33,3 % of participants had an SBA-HC titer ≥ 1:8 to serogroup A, and 0 – 2 % to serogroups C, Y and W135. After the second dose, percentages of participants with an SBA-HC titer ≥ 1:8 were: 85,2 %, serogroup A; 100,0 %, serogroup C; 96,3 %, serogroup Y; 96,2 %, serogroup W-135.

In the same study, a group of infants received MENACTRA vaccine at 9 months and 15 months of age (N=65). Prior to the first dose 43,9 % of participants had an SBA-HC titer ≥ 1:8 to serogroup A, and 0 – 2,2 % to serogroups C, Y and W-135. After the second dose, percentages of participants with an SBA-HC titer ≥ 1:8 were: 89,4 %, serogroup A; 100,0 %, serogroup C; 94,0 %, serogroup Y; 92,0%, serogroup W-135.

Immunogenicity in the population of meningococcal vaccinated naïve children 2 through 10 years of age.

The immunogenicity profile was demonstrated in a subset of 2 clinical trials with more than 750 children 2 through 10 years of age. Immunogenicity was assessed immediately before and 28 days after administration of a single dose of MENACTRA vaccine. Participants demonstrated a large increase in serum bactericidal antibodies resulting in a significant increase in SBA geometric mean titers (GMTs) from baseline values, for all four serogroups included in the vaccine, when measured 28 days post vaccination.

For all vaccine serogroups, 86 % to 100 % of participants with undetectable SBA titers (<1:8) at baseline seroconverted to achieve ≥ 4-fold rise in Day 28 SBA titers.

Immune responses induced by MENACTRA vaccine in monovalent C conjugate vaccinated children (non-naïve population)

The capacity of MENACTRA vaccine to induce a booster response to serogroup C polysaccharide and to prime for serogroups A, Y, and W-135 polysaccharides was documented by vaccinating children aged 3 to 5 years immunized during infancy with monovalent C conjugate meningococcal vaccines.

The immune responses against all four serogroups were of high magnitude, with high proportions of children developing a ≥ 4 - fold rise in their SBA-BR titers. In particular, responses against the serogroup C were strong with 93,2 % of children developing a ≥ 4 - fold rise in their SBA-BR titers. The data confirmed the lack of hyporesponsiveness induction by meningococcal conjugated vaccines.

Immunogenicity in the population adolescents 11 through 18 years of age

The immunogenicity profile was demonstrated in a subset of 2 clinical trials with approximately 1400 adolescents 11 through 18 years of age.

Results from a clinical trial conducted in adolescents 11 through 18 years of age, demonstrated a strong immune response to a single dose of MENACTRA vaccine SBA GMTs were significantly higher 28 days after vaccination than at baseline.

In addition, 98 % to 100 % of adolescents with undetectable SBA titer (<1:8) at baseline achieved a ≥ 4-fold rise in Day 28 SBA titers to all vaccine serogroups.

Immunogenicity in the population 18 through 55 years of age

The immunogenicity profile was demonstrated in a subset of three clinical trials and with more than 3,000 adolescents and adults. Immunogenicity was assessed immediately before and 28 days after administration of a single dose of MENACTRA vaccine Participants demonstrated a large increase in serum bactericidal antibodies resulting in a significant increase in SBA geometric mean titers (GMTs) from baseline values, for all four serogroups included in the vaccine, when measured 28 days post vaccination.

For all vaccine serogroups, 93 % to 100 % of participants with undetectable SBA titers (<1:8) at baseline achieved a ≥ 4-fold rise in Day 28 SBA titers.

Kinetics of the immune response

There are no data on the kinetics of the response with MENACTRA vaccine, but as with other polysaccharide and conjugate vaccines, it is estimated that protection is usually obtained 7 to 10 days after vaccination.

Duration of protection

No data available at this time.

However, the T-dependent response elicited by other conjugate vaccines has been demonstrated to provide immunological memory.

Protection through memory is expected to persist for several years, as per conjugate vaccines in general.

Efficacy

Clinical efficacy trials have not been performed as the induction of serum bactericidal antibodies has been established as a marker of efficacy for meningococcal vaccines. Data obtained during the vaccination campaign conducted in 1999 - 2000 in the UK, with three Meningococcal

serogroup C conjugates, have shown that a SBA titer of ≥ 8, using baby rabbit serum as source of complement correlates with protection. However, for other serogroups, the minimum protective SBA titer against meningococcal disease has not been determined.

Studies conducted with the Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined, Menomune® - A/C/Y/W-135, demonstrated that a 4-fold increase in bactericidal antibodies is indicative of protection in adults.

MENACTRA vaccine has been evaluated by assessing the production of specific functional antibodies according to the same serological criteria considered to be surrogate markers of protection.

INDICATIONS:

MENACTRA vaccine is indicated for active immunisation in individuals from 9 months through 55 years of age for prevention of invasive disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135.

MENACTRA vaccine is not to be used for treatment of meningococcal infections.

Meningococcal vaccination is also recommended for use in the control of meningococcal outbreaks.

MENACTRA vaccine can be used to boost the serogroup C antibody response in subjects primed with a monovalent C conjugate vaccine.

Please refer to national recommendations for high-risk groups.

CONTRAINDICATIONS:

Hypersensitivity

Known systemic hypersensitivity reaction to any component (i.e. as defined under sections Composition and Warnings) of MENACTRA vaccine or after previous administration of the vaccine or a vaccine containing the same components.

Febrile or acute disease

Generally vaccination must be postponed in cases of moderate or severe febrile and/or acute disease and low-grade fever does not constitute a contraindication.

WARNINGS AND SPECIAL PRECAUTIONS:

Warnings

Protection

MENACTRA vaccine will only protect against *N meningitidis* A, C, Y and W-135 serogroups and will not protect against any other microorganisms.

As with any vaccine, vaccination with MENACTRA may not protect 100 % of individuals against vaccine serogroups.

Individuals with functional or anatomical asplenia may produce an immune response to MENACTRA vaccine; however, the degree of protection that would be afforded is unknown.

Although an antibody response to diphtheria toxoid may occur, MENACTRA vaccine should not be considered as an immunising agent against diphtheria. No changes in the schedule for administering routine vaccines containing diphtheria toxoid are recommended.

Special patient groups

- **Thrombocytopenia or bleeding disorders**

  MENACTRA vaccine has not been evaluated in persons with thrombocytopenia or bleeding disorders. As with any other vaccine administered intramuscularly, the vaccine risk versus benefit for persons at risk of haemorrhage following intramuscular injection must be evaluated. If the decision is made to administer any product by intramuscular injection to such persons, it should be given with caution, with steps taken to avoid the risk of haematoma formation following injection.

- **Immunosuppression**

  No data are available on the use of MENACTRA vaccine in immunodeficient individuals.

  The immunogenicity of MENACTRA vaccine could be reduced by immunosuppressive treatment. In such cases it is recommended to postpone the vaccination until the end of the immunosuppression. Nevertheless, vaccination of individuals with chronic immunodeficiency such as HIV infection is recommended even if the antibody response might be limited.

- **Guillain-Barré Syndrome (GBS)**

  Persons previously diagnosed with Guillain-Barré syndrome (GBS) may be at increased risk of GBS following receipt of MENACTRA vaccine. The decision to give MENACTRA vaccine should take into account the potential benefits and risks.

  GBS has been reported in a temporal relationship following administration of MENACTRA vaccine. The risk of GBS following MENACTRA vaccination was evaluated in a post-marketing retrospective cohort study (refer to section Data from Post-Marketing surveillance).

Special Precautions

Administration route-related precautions

- **Administration of MENACTRA vaccine and DTaP**

  In cases where MENACTRA vaccine and DTaP vaccine are to be administered at 4 through 6 years of age, preference should be given to simultaneous administration of the 2 vaccines or administration of MENACTRA vaccine prior to DTaP vaccine. (Refer to Interactions).

Do not administer by intravascular injection: ensure that the needle does not penetrate a blood vessel.

Serious and severe adverse event related precautions

- **Anaphylactic reaction or serious adverse event**

  Prior to administration of any dose of MENACTRA vaccine, the parent or guardian of the recipient or the adult recipient himself must be asked about his personal history, family history, and recent health status, including immunisation history, current health status and any adverse event after previous immunisations. In subjects who have a history of serious or severe reaction within 48 hours of a previous injection with a vaccine containing similar components, the decision to vaccinate must be carefully considered.

  Before the injection of any biological, the person responsible for administration must take all precautions known for the prevention of allergic or any other reactions. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following administration of the vaccine.

  As a precautionary measure, epinephrine injection (1:1000) must be immediately available in case of unexpected anaphylactic or serious allergic reactions.

- **Pregnancy**

Refer to section PREGNANCY AND LACTATION.

- **Syncope**

Syncope (fainting) has been reported following vaccination with MENACTRA vaccine. Procedures should be in place to prevent falling injury and manage syncopal reactions.

INTERACTIONS:

Concomitant administration with other vaccines

Safety and immunogenicity of MENACTRA vaccine and co-administration with one or more of the following vaccines [Pneumococcal 7 valent Conjugate Vaccine (PCV), Measles, Mumps, and Rubella Virus Vaccine (MMR), Varicella Virus Vaccine live (V), Measles, Mumps, Rubella

and Varicella Virus Vaccine live (MMRV), Hepatitis A Vaccine (Hep A) or *Haemophilus influenzae* type b (Hib)] were evaluated in children younger than 2 years of age.

MENACTRA vaccine administered concomitantly had similar safety profiles compared to these vaccines given separately at 12 months of age.

In one clinical trial conducted in children 4 - 6 years of age, Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) (DAPTACEL/TRIPACEL/TRIACEL) and Menactra had similar safety profiles and were well tolerated when administered concomitantly or separately. Significantly lower antibody responses to all 4 meningococcal serogroups were observed when MENACTRA vaccine was administered 1 month after DTaP (DAPTACEL/TRIPACEL/TRIACEL). As a measure of precaution, in cases where MENACTRA vaccine and DTaP vaccine are to be administered at 4 through 6 years of age, preference should be given to simultaneous administration of the 2 vaccines or administration of MENACTRA vaccine prior to DTaP vaccine (see **SPECIAL PRECAUTIONS).**

MENACTRA vaccine can be administered concomitantly with typhoid Vi polysaccharide (Vi) or Tetanus and Diphtheria (Td) vaccines to adolescents and adults.

MENACTRA vaccine can be administered with bivalent or quadrivalent Human Papillomavirus (HPV) vaccines.

MENACTRA vaccine must not be mixed with any vaccine in the same syringe. Separate injection sites should be used in case of concomitant administration.

Vaccine-drug and / or vaccine-vaccine interactions

- Immunosuppressive therapy

If the vaccine is used in persons under immunosuppressive therapy, the expected immune response may not be obtained.

PREGNANCY AND LACTATION:

Pregnancy

Animal reproduction studies have not demonstrated a risk with respect to effects on pregnancy and embryo-foetal development, parturition and postnatal development. However, no studies have been performed in pregnant women and spontaneously reported post-marketing data on the use of this vaccine in pregnant women are limited. MENACTRA vaccine should be given to a pregnant woman only if clearly needed, such as during an outbreak or prior to necessary travel to an endemic area and only following an assessment of the risks and benefits.

Considering the severity of the meningococcal disease, pregnancy should not preclude vaccination when the risk/ benefit ratio of administering MENACTRA vaccine is considered favourable.

Lactation

It is not known whether the active substances included in the vaccine are excreted in human milk, but antibodies to the polysaccharides have been found to be transferred to the suckling offspring of mice.

Animal studies conducted in mice have not shown any harmful effect on the postnatal development of offspring exposed through breastfeeding to MENACTRA vaccine-induced maternal antibodies.

However, the effect on breast-fed infants of the administration of MENACTRA vaccine to their mothers has not been studied. The risks and benefits of vaccination should be assessed before making the decision to immunise a nursing woman.

DOSAGE AND DIRECTIONS FOR USE:

MENACTRA vaccine should be administered as a 0,5 mL dose by intramuscular injection preferably in the anterolateral thigh or deltoid region depending on the recipient’s age and Muscle mass.

Primary vaccination

In children 9 through 23 months of age, MENACTRA vaccine is given as a 2-dose series at least three months apart.

Individuals 2 through 55 years of age receive a single dose.

The vaccine should be inspected visually for any particulate matter and/or variation of physical aspect prior to administration. Do not use if the content appears otherwise.

Do not administer by intravascular injection.

Avoid injecting the vaccine intradermally or subcutaneously since clinical studies have not been done to establish safety and efficacy of the vaccine using these routes of administration.

Concomitant administration with other vaccines: refer to INTERACTIONS.

SIDE EFFECTS

Data from clinical studies

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

Studies conducted in subjects 11 through 55 years of age

The safety profile of MENACTRA vaccine comes from over 7,000 adolescents and adults (11 through 55 years old) enrolled in seven clinical trials.

Safety was evaluated within the first 7 days, 28 days, and 6 months after vaccination.

MENACTRA vaccine was generally safe and well tolerated among adolescents and adults.

The majority of the solicited local and systemic reactions reported within 7 days after vaccination were mild, with a mean duration of 2 days for the local reactions and less than 5 days for the systemic reactions.

The most commonly reported solicited adverse reactions were pain at the injection site and headache (respectively 55 % and 37 % in the whole population). **See Table 1**

MENACTRA vaccine was well tolerated in persons who had high pre-existing titers for any serogroup in this vaccine.

The overall safety profile was similar when evaluated by age, gender and race.

The overall safety profile for MENACTRA vaccine was comparable to the safety profile of the quadrivalent polysaccharide vaccine Menomune® - A/C/Y/W-135. However, local solicited reactions were more frequently reported for MENACTRA vaccine.

Table 1: Percentage of individuals reporting at least one solicited reaction within 7 days following vaccination with MENACTRA vaccine, by age category.

Event	**All Participants (11 through 55 years) N* = 7570**	**Age Category 11 through 14 years N* = 1625**	**Age Category 15 through 25 years N* = 4019**	**Age Category 26 through 55 years N* = 1926**
Local (Injection site)				
Pain at the injection site	54,6	56,2	60,2	41,7
Induration	16,5	17,4	17,4	14,0
Redness	12,3	13,2	12,3	11,7
Swelling	11,8	14,2	11,2	10,9
Systemic				
Headache	37,3	31,6	39,9	36,7
Fatigue	31,0	25,8	33,5	30,1

Malaise	21,7	18,7	23,5	20,2
Arthralgia	18,1	16,7	19,7	16,0
Diarrhoea	12,6	8,9	13,6	13,8
Anorexia	10,8	10,5	11,3	9,8
Chills	7,6	7,7	7,9	7,1
Fever >99,5 °F	6,1	8,1	5,5	5,4
Vomiting	2,1	2,8	2,1	1,7
Rash	1,5	2,0	1,4	1,2

N*= Total number of participants with data, in each age group, in all clinical trials

Studies conducted in subjects 2 through 10 years of age

The safety profile of MENACTRA vaccine was evaluated in over 2400 children ages 2 through 10 years enrolled in three clinical trials. Two of the studies documented the safety profile of MENACTRA vaccine in meningococcal vaccination naïve population. The third study documented the safety profile of MENACTRA vaccine used as a meningococcal (re) vaccination in children already vaccinated with meningococcal C conjugated vaccine (non-naïve population). The safety profile of MENACTRA vaccine is reported separate for these two populations.

Safety was evaluated within the first 7 days, 28 days and 6 months after vaccination.

MENACTRA vaccine was generally safe and well tolerated among children.

The majority of the solicited local and systemic reactions reported within 7 days after vaccination were mild, with a mean duration of no more than 3 days for the local reactions and less than 4 days for the systemic reactions.

Safety profile of MENACTRA vaccine when used in meningococcal vaccination naïve population

The most commonly reported solicited adverse reaction was pain at the injection site (40 % to 48 % of the participants). **See Table 2 below.**

Table 2: Percentage of individuals reporting at least one solicited reaction within 7 days following vaccination with MENACTRA vaccine, by study.

	Study 1	**Study 2**		
	US ***N[a] =674-693***	***US*** ***N[a]=1154-1157***	***Chilean*** ***N[a]=536-548***	***All subjects*** ***N[a]=1690-1705***
	%	*%*	*%*	%
Local				
Redness	29,5	*21,8*	*9,7*	17,9
Swelling	20,5	*17,4*	*7,7*	14,3
Induration	22,1	*18,9*	*10,2*	16,1
Pain	48,1	*45,0*	*28,5*	39,7
Systemic				
Fever	11,4	5,2	7,3	5,9
Irritability[b]	35,2	12,4	8,0	11,0
Drowsiness	26,0	10,8	9,5	10,4
Anorexia	22,7	8,2	8,6	8,3
Vomiting	5,9	3,0	4,4	3,5
Diarrhoea	15,9	11,1	14,2	12,1
Arthralgia	-	6,8	8,2	7,3
Hives	1,2	-	-	-
Rash	-	3,4	5,7	4,1
Seizures	-	0,0	0,0	0,0

N[a] = The total number of participants with data

b = Irritability was collected in Study 1 under Fussiness

- **Safety profile of MENACTRA vaccine when used in meningococcal vaccination non naïve population**

  A clinical study MTA15 performed in the UK documented the safety profile of MENACTRA vaccine compared to *Haemophilus influenzae* Type b (Hib) vaccine Hiberix®, a lyophilised vaccine of purified polyribosyl-ribitol-phosphate (PRP) capsular polysaccharide of Hib, covalently bound to tetanus toxoid, when used in children (mean age of 3 years) already vaccinated with a meningococcal protein-conjugated monovalent C vaccine.

  The majority of the solicited injection site (local) and systemic reactions reported within 7 days after vaccination were mild, with a mean duration of 3 days.

  The most commonly reported solicited adverse reaction was irritability (reported by 57 % of the participants). **See Table3 below.**

Table: 3 Percentage of meningococcal vaccination non-naïve individuals reporting at least one solicited reaction within 7 days following vaccination with MENACTRA

Event	**MENACTRA®**	**Hiberix®**
	N[a]=51	**N[a]=49**
Local		
Redness	41,2	34,7
Swelling	35,3	22,4
Induration	37,3	24,5
Pain	35,3	34,7
Systemic		

Event	MENACTRA®	Hiberix®
Fever	8,5	6,8
Irritability	56,9	34,7
Drowsiness	35,3	20,4
Anorexia	37,3	20,4
Vomiting	7,8	4,1
Diarrhoea	11,8	16,3
Rash	5,8	10,2
Seizures	2,0	0,0

N[a] = The total number of subjects reporting at least one solicited reaction. The median age of participants was 6 years in both vaccine groups.

Studies conducted in subjects 9 months through 18 months of age

The safety profile of MENACTRA vaccine comes from approximately 3700 infants (9 months through 18 months) enrolled in four clinical trials.

Safety was evaluated within the first 7 days, 30 days, and 6 months after the last vaccination.

Two doses of Menactra vaccine are safe and well tolerated by infants and toddlers when given alone or with concomitant vaccines (refer to Table 4 for a list of concomitant vaccines).

The majority of the solicited local reactions reported within 7 days after vaccination were of Grade 1 or Grade 2 intensity and of short duration (≤ 3 days). The majority of the solicited systemic reactions were of Grade 1 intensity and of short duration (≤ 3 days). See Table 4 and Table 5.

Table 4: Any and Grade 3 Solicited Injection Site Reactions That Occurred at the MENACTRA Vaccine Injection Site within 7 Days after Vaccination (Safety Population - All)

		Age at Vaccination				
		9 Months	12 Months			
		Menactra vaccine (N[a] =3267)	Menactra vaccine (N[a] =632)	Menactra vaccine + MMRV (N[a] =825)	Menactra vaccine + PCV (N[a]=621)	Menactra vaccine + MMRV +PCV+HepA (N[a]=938)
Subjects with:	**Intensity**	**%**	**%**	**%**	**%**	**%**
Any Reaction	**Any**	46,8	43,2	46,8	54,6	57,5
	Grade 3	1,7	2,0	3,7	3,9	1,4
Tenderness	**Any**	34,9	35,2	38,1	48,9	48,5
	Grade 3	0,4	0,3	0,8	1,2	1,3
Erythema	**Any**	24,5	23,3	24,2	26,6	30,1
	Grade 3	1,0	1,5	2,6	2,8	0,1
Swelling	**Any**	13,2	11,1	13,4	16,1	16,2
	Grade 3	0,5	0,8	1,5	1,2	0,1

[a] N is the total number of vaccinated subjects in each group.

Table 5: Any and Grade 3 Solicited Systemic Reactions that Occurred Within 7 Days After Vaccination (Safety Population - All)

		Age at Vaccination						
		9 Months	12 Months					
		Menactra vaccine (N[a]=3267)	Menactra vaccine (N[a]=632)	Menactra vaccine +MMRV (N[a]=825)	Menactra vaccine +PCV (N[a]=621)	MMRV+ PCV (N[a]=476)	Menactra vaccine +MMRV +PCV+HepA (N[a]=938)	MMRV+PCV+ HepA (N[a]=321)
Subjects with:	**Intensity**	**%**	**%**	**%**	**%**	**%**	**%**	**%**
Any Reaction	**Any**	68,2	60,6	71,1	68,3	76,6	73,2	75,2
	Grade 3	5,6	5,7	8,0	7,0	8,1	7,6	7,5
Fever Any Route[b]	**Any**	12,4	13,7	22,4	20,2	24,3	24,5	21,8
	Grade 3	1,0	0,7	2,7	1,7	2,4	1,9	2,0
Vomiting	**Any**	14,3	7,1	10,4	9,7	9,6	11,0	9,8
	Grade 3	0,4	0,8	0,6	0,0	0,2	0,2	0,0
Crying Abnormal	**Any**	34,2	30,1	40,2	37,0	38,6	40,0	39,4
	Grade 3	2,1	1,9	2,3	3,5	2,4	2,3	0,7
Drowsiness	**Any**	31,1	27,2	32,1	33,1	39,1	39,8	39,1
	Grade 3	0,7	0,3	0,9	0,8	1,5	1,1	0,7
Appetite Lost	**Any**	27,3	25,4	31,9	29,7	29,3	35,7	31,9
	Grade 3	0,9	1,9	1,5	2,0	1,5	2,2	0,7
Irritability	**Any**	55,4	48,5	58,7	58,3	62,4	62,1	64,8
	Grade 3	2,6	3,0	3,3	4,2	3,5	3,5	4,2

N[a] is the total number of vaccinated subjects in each group. [b] Intensity scale for fever: Any (> 38 °C) and Grade 3 (> 39,5 °C).

Data from Post-marketing surveillance

Based on spontaneous reporting, the following additional adverse events have been reported following commercial use of MENACTRA vaccine. These events have been **very rarely** reported, however exact incidence rates cannot be calculated precisely, their frequency is qualified as "Not known".

- **Immune system disorders**

  Hypersensitivity reactions such as anaphylaxis/anaphylactic, wheezing, difficulty breathing, upper airway swelling, urticaria, erythema, pruritus, hypotension.

- **Nervous system disorders**

  Guillain-Barré syndrome, paraesthesia, vasovagal syncope, dizziness, convulsion, facial palsy, acute disseminated encephalomyelitis, transverse myelitis.

- **Musculoskeletal and connective tissue disorders**

  Myalgia

Post-marketing safety study

The risk of GBS following receipt of MENACTRA vaccine was evaluated in a US retrospective cohort study using healthcare claims data from 9,578,688 individuals 11 through 18 years of age, of whom 1,431,906 (15 %) received MENACTRA vaccine. Of 72 medical chart-confirmed GBS cases, none had received MENACTRA vaccine within 42 days prior to symptom onset. An additional 129 potential cases of GBS could not be confirmed or excluded due to absent or insufficient medical chart information. In an analysis that took into account the missing data, estimates of the attributable risk of GBS ranged from 0 to 5 additional cases of GBS per 1,000,000 vaccines within the 6 week period following vaccination.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

None known

IDENTIFICATION:

MENACTRA vaccine is a clear to slightly turbid solution in unit dose vials, without preservative and free of particulate matter. Do not use if contents appears otherwise.

PRESENTATION:

The vaccine is available in a 0,5 ml type 1 borosilicate clear glass vial with a grey chlorobutyl synthetic polyisoprene blend (not made with natural rubber latex) stopper and aluminium flip off cap made of aluminium skirt that is fitted with white plastic cap.

1 vial is packed in 1 carton

STORAGE INSTRUCTIONS:

Store at +2 °C to +8 °C (i.e., in a refrigerator). DO NOT FREEZE.

Discard product if it has been exposed to freezing.

STORE IN OUTER CARTON UNTIL BEFORE USE.

Do not use after expiration date.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

44/30.1/1064

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

sanofi-aventis south Africa (pty)

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SADC INFORMATION

Namibia

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