

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

### **Menactra®**

#### **FOR INTRAMUSCULAR INJECTION**

#### **INDICATIONS AND USAGE**

Menactra®, Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine, is indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135. Menactra is approved for use in individuals 9 months through 55 years of age. Menactra does not prevent *N meningitidis* serogroup B disease.

#### **DOSAGE AND ADMINISTRATION**

##### **Preparation for Administration**

Menactra is a clear to slightly turbid solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If any of these conditions exist, the vaccine should not be administered.

Withdraw the 0.5 mL dose of vaccine from the single-dose vial using a sterile needle and syringe.

##### **Dose and Schedule**

Menactra is administered as a single 0.5 mL dose by **intramuscular** injection, preferably in the anterolateral thigh or deltoid region depending on the recipient's age and muscle mass.

Do not administer this product intravenously or subcutaneously.

##### **Primary Vaccination:**

- In children 9 through 23 months of age, Menactra is given as a 2-dose series at least three months apart.
- Individuals 2 through 55 years of age, Menactra is given as a single dose.

##### **Booster Vaccination:**

- A single booster dose may be given to individuals 15 through 55 years of age at continued risk for meningococcal disease, if at least 4 years have elapsed since the prior dose.

#### **DOSAGE FORMS AND STRENGTHS**

Menactra is a solution supplied in 0.5 mL single-dose vials. [See **DESCRIPTION** for a complete listing of ingredients.]

## **CONTRAINDICATIONS**

### **Hypersensitivity**

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of a meningococcal capsular polysaccharide-, diphtheria toxoid- or CRM<sub>197</sub>-containing vaccine, or to any component of Menactra [see **DESCRIPTION**].

### **Febrile or Acute Disease**

Vaccination should be postponed in case of febrile or acute disease that is moderate or severe. However, a minor febrile or non-febrile illness, such as mild upper respiratory infection, is not usually a valid reason to postpone immunization.

## **WARNINGS AND PRECAUTIONS**

### **Guillain-Barré Syndrome**

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

GBS has been reported in temporal relationship following administration of Menactra. The risk of GBS following Menactra vaccination was evaluated in a post-marketing retrospective cohort study [see **Post-Marketing Experience, Post-Marketing Safety Study**].

### **Preventing and Managing Allergic Vaccine Reactions**

Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an assessment of benefits and risks. Epinephrine and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

### **Thrombocytopenia or Bleeding Disorders**

Menactra 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 hemorrhage following intramuscular injection must be evaluated.

### **Altered Immunocompetence**

- *Reduced Immune Response*

Some individuals with altered immunocompetence, including some individuals receiving immunosuppressant therapy, may have reduced immune responses to Menactra.

- *Complement Deficiency*

Persons with certain complement deficiencies and persons receiving treatment that inhibits terminal complement activation (for example, eculizumab) are at increased risk for invasive disease caused by *N meningitidis*, including invasive disease caused by serogroups A, C, Y and W-135, even if they develop antibodies following vaccination with Menactra. [See **Clinical Pharmacology**.]

### **Limitations of Vaccine Effectiveness**

Menactra may not protect all recipients.

### **Syncope**

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

## **ADVERSE REACTIONS**

### **Clinical Trials Experience**

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

#### ***Children 9 Through 12 Months of Age***

The safety of Menactra was evaluated in four clinical studies that enrolled 3721 participants who received Menactra at 9 and 12 months of age. At 12 months of age, these children also received one or more other vaccines [Measles, Mumps, Rubella and Varicella Virus Vaccine Live (MMRV) or Measles, Mumps, and Rubella Virus Vaccine (MMR) and Varicella Virus Vaccine Live (V); Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM<sub>197</sub> Protein) (PCV7); Hepatitis A Vaccine (HepA)]. A control group of 997 children was enrolled at 12 months of age and received two or more childhood vaccines [MMRV (or MMR + V), PCV7, HepA] at 12 months of age [see **Concomitant Vaccine Administration**]. Three percent of individuals received MMR and V, instead of MMRV, at 12 months of age.

The primary safety study was a controlled trial that enrolled 1256 children who received Menactra at 9 and 12 months of age. At 12 months of age, these children received MMRV (or MMR + V), PCV7, and HepA. A control group of 522 children received MMRV, PCV7, and HepA. Of the 1778 children, 78% of participants (Menactra, N = 1056; control group, N = 322) were enrolled at United States (US) sites and 22% at a Chilean site (Menactra, N = 200; control group, N = 200).

## ***Individuals 2 Through 55 Years of Age***

The safety of Menactra was evaluated in eight clinical studies that enrolled 10,057 participants aged 2 – 55 years who received Menactra and 5266 participants who received Menomune<sup>®</sup> – A/C/Y/W-135, Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined. There were no substantive differences in demographic characteristics between the vaccine groups. Among Menactra recipients 2 – 55 years of age 24.0%, 16.2%, 40.4% and 19.4% were in the 2 – 10, 11 – 14, 15 – 25 and 26 – 55 year age groups, respectively. Among Menomune – A/C/Y/W-135 recipients 2 – 55 years of age 42.3%, 9.3%, 30.0% and 18.5% were in the 2 – 10, 11 – 14, 15 – 25 and 26 – 55-year age groups, respectively. The three primary safety studies were randomized, active-controlled trials that enrolled participants 2 – 10 years of age (Menactra, N = 1713; Menomune – A/C/Y/W-135, N = 1519), 11 – 18 years of age (Menactra, N = 2270; Menomune – A/C/Y/W-135, N = 972), and 18 – 55 years of age (Menactra, N = 1384; Menomune – A/C/Y/W-135, N = 1170), respectively. Of the 3232 children 2 - 10 years of age, 68% of participants (Menactra, N = 1164; Menomune – A/C/Y/W-135, N = 1031) were enrolled at US sites and 32% (Menactra, N = 549; Menomune – A/C/Y/W-135, N = 488) of participants at a Chilean site. The median ages in the Chilean and US subpopulations were 5 and 6 years, respectively. All adolescents and adults were enrolled at US sites. As the route of administration differed for the two vaccines (Menactra given intramuscularly, Menomune – A/C/Y/W-135 given subcutaneously), study personnel collecting the safety data differed from personnel administering the vaccine.

### **Booster Vaccination Study**

In an open-label trial conducted in the US, 834 individuals were enrolled to receive a single dose of Menactra 4 – 6 years after a prior dose. The median age of participants was 17.1 years at the time of the booster dose.

### **Safety Evaluation**

Participants were monitored after each vaccination for 20 or 30 minutes for immediate reactions, depending on the study. Solicited injection site and systemic reactions were recorded in a diary card for 7 consecutive days after each vaccination. Participants were monitored for 28 days (30 days for infants and toddlers) for unsolicited adverse events and for 6 months post-vaccination for visits to an emergency room, unexpected visits to an office physician, and serious adverse events (SAEs). Unsolicited adverse event information was obtained either by telephone interview or at an interim clinic visit. Information regarding adverse events that occurred in the 6-month post-vaccination time period was obtained via a scripted telephone interview.

### **Serious Adverse Events in All Safety Studies**

Serious adverse events were reported during a 6-month time period following vaccinations in individuals 9 months through 55 years of age. In children who received Menactra at 9 months and at 12 months of age, SAEs occurred at a rate of 2.0% - 2.5%. In participants who received one or more childhood vaccine(s) (without co-administration of Menactra) at 12 months of age, SAEs occurred at a rate of 1.6% - 3.6%, depending on the number and type of vaccines received.

In children 2 – 10 years of age, SAEs occurred at a rate of 0.6% following Menactra and at a rate of 0.7% following Menomune – A/C/Y/W-135. In adolescents 11 through 18 years of age and adults 18 through 55 years of age, SAEs occurred at a rate of 1.0% following Menactra and at a rate of 1.3% following Menomune – A/C/Y/W-135. In adolescents and adults, SAEs occurred at a rate of 1.3% following booster vaccination with Menactra.

### **Solicited Adverse Events in the Primary Safety Studies**

The most frequently reported solicited injection site and systemic adverse reactions within 7 days following vaccination in children 9 months and 12 months of age were injection site tenderness and irritability.

The most frequently reported solicited local and systemic adverse reactions in US children aged 2 – 10 years were injection site pain and irritability. Diarrhea, drowsiness, and anorexia were also common. The most commonly reported solicited injection site and systemic adverse reactions in adolescents, ages 11 – 18 years, and adults, ages 18 – 55 years, after a single dose were injection site pain, headache, and fatigue. Except for redness in adults, injection site reactions were more frequently reported after Menactra vaccination than after Menomune – A/C/Y/W-135 vaccination.

### **Solicited Adverse Events in a Booster Vaccination Study**

For a description of the study design and number of participants, [see **Clinical Trials Experience, Booster Vaccination Study**]. The most common solicited injection site and systemic reactions within 7 days of vaccination were pain (60.2%) and myalgia (42.8%), respectively. Overall rates of solicited injection site reactions and solicited systemic reactions were similar to those observed in adolescents and adults after a single Menactra dose. The majority of solicited reactions were Grade 1 or 2 and resolved within 3 days.

### **Adverse Events in Concomitant Vaccine Studies**

#### ***Solicited Injection Site and Systemic Reactions When Given With Other Pediatric Vaccines***

For a description of the study design and number of participants [see **Clinical Trials Experience, Concomitant Vaccine Administration**]. In the primary safety study, 1378 US children were enrolled to receive Menactra alone at 9 months of age and Menactra plus one or more other routinely administered vaccines (MMRV, PCV7, and HepA) at 12 months of age (N = 961). Another group of children received two or more routinely administered vaccines (MMRV, PCV7, and HepA vaccines) (control group, N = 321) at 12 months of age. Participants who received Menactra and the concomitant vaccines at 12 months of age described above reported similar frequencies of tenderness, redness, and swelling at the Menactra injection site and at the concomitant vaccine injection sites. Tenderness was the most frequent injection site reaction (48%, 39%, 46%, and 43% at the Menactra, MMRV, PCV7, and HepA sites, respectively). Irritability was the most frequent systemic reaction, reported in 62% of recipients of Menactra plus concomitant vaccines, and 65% of the control group. [See **Concomitant Vaccine Administration**.]

In a randomized, parallel group, US multi-center clinical trial conducted in children 4 through 6 years of age, Menactra was administered as follows: 30 days after concomitant DAPTACEL<sup>®</sup>, Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, (DTaP), manufactured by Sanofi Pasteur Limited + IPOL<sup>®</sup>, Poliovirus Vaccine Inactivated, (IPV), manufactured by Sanofi Pasteur SA [Group A]; concomitantly with DAPTACEL followed 30 days later by IPV [Group B]; concomitantly with IPV followed 30 days later by DAPTACEL [Group C]. Solicited injection site and systemic reactions were recorded in a diary card for 7 consecutive days after each vaccination. For all study groups, the most frequently reported solicited local reaction at the Menactra site was pain: 52.2%, 60.9% and 56.0% of participants in Groups A, B and C, respectively. For all study groups, the most frequently reported systemic reaction following the administration of Menactra alone or with the respective concomitant vaccines was myalgia: 24.2%, 37.3% and 26.7% of participants in Groups A, B and C, respectively. Fever >39.5°C occurred at < 1.0% in all groups. [See **Concomitant Vaccine Administration.**]

#### ***Solicited Injection Site and Systemic Reactions When Given With Tetanus and Diphtheria Toxoid Adsorbed Vaccine (Td)***

In a clinical study, rates of local and systemic reactions after Menactra and Tetanus and Diphtheria Toxoid Adsorbed (Td) vaccine manufactured by Sanofi Pasteur Inc. were compared [see **Drug Interactions** and **Concomitant Vaccine Administration** for study description].

Injection site pain was reported more frequently after Td vaccination than after Menactra vaccination (71% versus 53%). The overall rate of systemic adverse events was higher when Menactra and Td vaccines were given concomitantly than when Menactra was administered 28 days after Td vaccine (59% versus 36%). In both groups, the most common reactions were headache (Menactra + Td vaccine, 36%; Td vaccine + Placebo, 34%; Menactra alone, 22%) and fatigue (Menactra + Td vaccine, 32%; Td vaccine+ Placebo, 29%; Menactra alone, 17%). Fever ≥ 40.0°C occurred at ≤ 0.5% in all groups.

#### ***Solicited Injection Site and Systemic Reactions When Given With Typhoid Vi Polysaccharide Vaccine***

In a clinical study, rates of local and systemic reactions after Menactra and Typhim Vi<sup>®</sup> [Typhoid Vi Polysaccharide Vaccine] (Typhoid), produced by Sanofi Pasteur SA were compared [see **Drug Interactions** and **Concomitant Vaccine Administration** for a description of the concomitantly administered vaccine, study design and number of participants].

More participants experienced pain after Typhoid vaccination than after Menactra vaccination (Typhoid + Placebo, 76% versus Menactra + Typhoid, 47%). The majority (70% -77%) of injection site solicited reactions for both groups at either injection site were reported as Grade 1 and resolved within 3 days post-vaccination. In both groups, the most common systemic reaction was headache (Menactra + Typhoid, 41%; Typhoid + Placebo, 42%; Menactra alone, 33%) and fatigue (Menactra + Typhoid, 38%; Typhoid + Placebo, 35%; Menactra alone, 27%). Fever ≥ 40.0°C and seizures were not reported in either group.

## **Post-Marketing Experience**

In addition to reports in clinical trials, worldwide voluntary adverse events reports received since market introduction of Menactra are listed below. This list includes serious events and/or events which were included based on severity, frequency of reporting or a plausible causal connection to Menactra. Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccination.

### **Blood and Lymphatic System Disorders**

Lymphadenopathy

### **Immune System Disorders**

Hypersensitivity reactions such as anaphylaxis/anaphylactic reaction, 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

### **General Disorders and Administrative Site Conditions**

Large injection site reactions, extensive swelling of the injected limb (may be associated with erythema, warmth, tenderness or pain at the injection site).

### **Post-Marketing Safety Study**

The risk of GBS following receipt of Menactra 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. Of 72 medical chart-confirmed GBS cases, none had received Menactra 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 vaccinees within the 6 week period following vaccination.

## **DRUG INTERACTIONS**

## **Concomitant Administration with Other Vaccines**

Menactra was concomitantly administered with Typhim Vi<sup>®</sup> [Typhoid Vi Polysaccharide Vaccine] (Typhoid) and Tetanus and Diphtheria Toxoids Adsorbed, For Adult Use (Td) vaccine, in individuals 18 through 55 and 11 through 17 years of age, respectively. In children 4 through 6 years of age, Menactra was co-administered with DAPTACEL, and in children younger than 2 years of age, Menactra vaccine was co-administered with one or more of the following vaccines: PCV7, MMR, V, MMRV or HepA vaccine [see **CLINICAL STUDIES** and **ADVERSE REACTIONS**].

When Menactra and DAPTACEL are to be administered to children 4 through 6 years of age, preference should be given to simultaneous administration of the 2 vaccines or administration of Menactra prior to DAPTACEL. Administration of Menactra one month after DAPTACEL has been shown to reduce meningococcal antibody responses to Menactra. Data are not available to evaluate the immune response to Menactra administered to younger children following DAPTACEL or to Menactra administered to persons < 11 years of age following other diphtheria toxoid-containing vaccines [see **CLINICAL STUDIES**].

When Menactra was administered concomitantly with PCV, antibody responses to 3 of the 7 serotypes in PCV and to serogroup W-135 of Menactra did not meet the non-inferiority criteria.

Do not mix Menactra with other vaccines in the same syringe. When Menactra is administered concomitantly with other injectable vaccines, the vaccines should be administered with different syringes and given at separate injection sites.

## **Immunosuppressive Therapies**

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune response to vaccines.

## **USE IN SPECIFIC POPULATIONS**

### **Pregnancy**

#### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Menactra during pregnancy.

#### Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. There are no adequate and well-controlled studies of Menactra administration in pregnant women in the US. Available data suggest that rates of major birth defects and miscarriage in women who received Menactra 30 days prior to pregnancy or during pregnancy are consistent with estimated background rates.

A developmental toxicity study was performed in female mice given 0.1 mL (in divided doses) of Menactra prior to mating and during gestation (a single human dose is 0.5 mL). The study revealed no evidence of harm to the fetus due to Menactra [see **Animal Data**].

## Data

### *Human Data*

A pregnancy registry spanning 11 years (2005-2016) included 222 reports of exposure to Menactra from 30 days before or at any time during pregnancy. Of these reports, 87 had known pregnancy outcomes available and were enrolled in the pregnancy registry prior to the outcomes being known. Outcomes among these prospectively followed pregnancies included 2 major birth defects and 6 miscarriages.

### *Animal Data*

A developmental toxicity study was performed in female mice. The animals were administered 0.1 mL of Menactra (in divided doses) at each of the following time points: 14 days prior to mating, and on Days 6 and 18 of gestation (a single human dose is 0.5 mL). There were no vaccine-related fetal malformations or variations, and no adverse effects on pre-weaning development observed in the study.

## **Lactation**

### Risk Summary

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Menactra and any potential adverse effects on the breastfed child from Menactra. Data are not available to assess the effects of Menactra on the breastfed infant or on milk production/excretion.

## **Pediatric Use**

Menactra is not approved for use in infants under 9 months of age. Available data show that infants administered three doses of Menactra (at 2, 4, and 6 months of age) had diminished responses to each meningococcal vaccine serogroup compared to older children given two doses at 9 and 12 months of age.

## **Geriatric Use**

Safety and effectiveness of Menactra in adults older than 55 years have not been established.

## **DESCRIPTION**

Menactra is a sterile, intramuscularly administered vaccine that contains *N meningitidis* serogroup A, C, Y and W-135 capsular polysaccharide antigens individually conjugated to diphtheria toxoid protein. *N meningitidis* A, C, Y and W-135 strains are cultured on Mueller Hinton agar and grown in Watson Scherp media containing casamino acid. The polysaccharides are extracted from the *N meningitidis* cells and purified by centrifugation, detergent precipitation,

alcohol precipitation, solvent extraction and diafiltration. To prepare the polysaccharides for conjugation, they are depolymerized, derivatized, and purified by diafiltration. Diphtheria toxin is derived from *Corynebacterium diphtheriae* grown in modified culture medium containing hydrolyzed casein and is detoxified using formaldehyde. The diphtheria toxoid protein is purified by ammonium sulfate fractionation and diafiltration. The derivatized polysaccharides are covalently linked to diphtheria toxoid and purified by serial diafiltration. The four meningococcal components, present as individual serogroup-specific glycoconjugates, compose the final formulated vaccine. No preservative or adjuvant is added during manufacture. Each 0.5 mL dose may contain residual amounts of formaldehyde of less than 2.66 mcg (0.000532%), by calculation. Potency of Menactra is determined by quantifying the amount of each polysaccharide antigen that is conjugated to diphtheria toxoid protein and the amount of unconjugated polysaccharide present.

Menactra is manufactured as a sterile, clear to slightly turbid liquid. Each 0.5 mL dose of vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution to contain 4 mcg each of meningococcal A, C, Y and W-135 polysaccharides conjugated to approximately 48 mcg of diphtheria toxoid protein carrier.

The vial stopper is not made with natural rubber latex.

## **CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

The presence of bactericidal anti-capsular meningococcal antibodies has been associated with protection from invasive meningococcal disease. Menactra induces the production of bactericidal antibodies specific to the capsular polysaccharides of serogroups A, C, Y and W-135.

## **NON-CLINICAL TOXICOLOGY**

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Menactra has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility. A developmental animal toxicity study showed that Menactra had no effects on female fertility in mice [see **Pregnancy**].

## **CLINICAL STUDIES**

### **Efficacy**

The Serum Bactericidal Assay (SBA) used to test sera contained an exogenous complement source that was either human (SBA-H) or baby rabbit (SBA-BR).

The response to Menactra vaccination administered to children 9 months through 10 years of age was evaluated by the proportion of participants having an SBA-H antibody titer of 1:8 or greater, for each serogroup. In individuals 11 through 55 years of age, the response to Menactra

vaccination was evaluated by the proportion of participants with a 4-fold or greater increase in baseline bactericidal antibody titers to each serogroup as measured by SBA-BR. For individuals 2 through 55 years of age, vaccine efficacy after a single dose was inferred from the demonstration of immunologic equivalence to a US-licensed meningococcal polysaccharide vaccine, Menomune – A/C/Y/W-135 vaccine as assessed by SBA.

## **Immunogenicity**

### ***Immunogenicity in Children 9 through 23 Months of Age***

In a randomized, US, multi-center trial, children received Menactra at 9 months and 12 months of age. The first Menactra dose was administered alone, followed by a second Menactra dose given alone (N = 404), or with MMRV (N = 302), or with PCV7 (N = 422). For all participants, sera were obtained approximately 30 days after last vaccination. There were no substantive differences in demographic characteristics between the vaccine groups. The median age for administration of the first dose of Menactra was approximately 9 months.

In the primary immunogenicity study, children received Menactra at 9 and 12 months of age, the majority of the participants in groups that received the second dose of Menactra alone or with concomitant pediatric vaccine(s), achieved SBA-HC titers  $\geq 1:8$  for all serogroups. Groups that received the second dose of Menactra alone had  $\geq 91\%$  of subjects achieving an SBA-HC titer  $\geq 1:8$  for serogroups A, C, and Y and  $\geq 86\%$  for serogroup W-135. When the second dose of Menactra was given concomitantly with MMRV (or MMRV + Hib) or with PCV, the percentages of subjects with SBA-HC titers  $\geq 1:8$  were high ( $> 90\%$  for serogroups A, C, and Y and  $> 81\%$  for serogroup W-135). SBA-HC geometric mean titers (GMTs) were high for all serogroups.

An additional study evaluating responses to 2-dose series of Menactra administered at either 9 and 15 months or at 12 and 15 months of age was conducted. Following the second dose of Menactra in the 9 - 15 months group, the percentages of participants with hSBA titer  $\geq 1:8$  were high for all of the serogroups ( $> 96\%$  for C, Y and W-135 and  $> 85.2\%$  for serogroup A). Similar responses were observed in the 12 - 15 months group. The percentages of participants with an hSBA titer  $\geq 1:8$  were: 85.2% for A; 100.0% for C and  $> 96\%$  for both Y and W-135 serogroups.

### ***Immunogenicity in Individuals 2 through 55 Years of Age***

Immunogenicity was evaluated in three comparative, randomized, US, multi-center, active controlled clinical trials that enrolled children (2 through 10 years of age), adolescents (11 through 18 years of age), and adults (18 through 55 years of age). Participants received a single dose of Menactra (N = 2526) or Menomune – A/C/Y/W-135 (N = 2317). For all age groups studied, sera were obtained before and approximately 28 days after vaccination. (Blinding procedures for safety assessments are described in **ADVERSE REACTIONS** section.)

In each of the trials, there were no substantive differences in demographic characteristics between the vaccine groups, between immunogenicity subsets or the overall study population. In the study of children 2 through 10 years of age, the median age of participants was 3 years; 95%

completed the study. In the adolescent trial, the median age for both groups was 14 years; 99% completed the study. In the adult trial, the median age for both groups was 24 years; 94% completed the study.

### ***Immunogenicity in Children 2 through 10 Years of Age***

Of 1408 enrolled children 2 through 10 years of age, immune responses evaluated by hSBA in a subset of Menactra participants (2 through 3 years of age, N = 52; 4 through 10 years of age, N = 84) and Menomune – A/C/Y/W-135 participants (2 through 3 years of age, N = 53; 4 through 10 years of age, N = 84), the percentages of subjects with a titer  $\geq$  1:8 were constantly higher in the Menactra group for all four serogroups.

In the evaluated subset of participants 2 through 3 years of age, the percentage of participants with an SBA-H titer  $\geq$  1:8 at Day 28 were 73%, Serogroup A; 63%, Serogroup C; 88%, Serogroup Y; 63%, Serogroup W-135 in the Menactra group and 64%, Serogroup A; 38%, Serogroup C; 73%, Serogroup Y; and 33%, Serogroup W-135 in the Menomune-A/C/Y/W-135 group.

In the evaluated subset of participants 4 through 10 years of age, the percentage of participants with an SBA-H titer  $\geq$  1:8 at Day 28 were 81%, Serogroup A; 79%, Serogroup C; 99%, Serogroup Y; 85%, Serogroup W-135 in the Menactra group and 55%, Serogroup A; 48%, Serogroup C; 92%, Serogroup Y; and 79%, Serogroup W-135 in the Menomune-A/C/Y/W-135 group.

### ***Immunogenicity in Adolescents 11 through 18 Years of Age***

Results from the comparative clinical trial conducted in 881 adolescents (aged 11 through 18 years) showed that the immune responses to Menactra and Menomune – A/C/Y/W-135 were similar for all four serogroups.

The percentage of participants with an SBA-BR titer with a  $\geq$  4-fold rise from the baseline were 93%, Serogroup A; 92%, Serogroup C; 82%, Serogroup Y; 97%, Serogroup W-135 in the Menactra group and 92%, Serogroup A; 89%, Serogroup C; 80%, Serogroup Y; and 95%, Serogroup W-135 in the Menomune-A/C/Y/W-135 group.

In participants with undetectable pre-vaccination titers (i.e., SBA-BR titers  $<$  1:8 at Day 0), seroconversion rates (defined as the proportions of participants achieving a  $\geq$  4-fold rise in SBA-BR titers by Day 28) were similar between the Menactra and Menomune – A/C/Y/W-135 recipients. Menactra participants achieved seroconversion rates of: 100%, Serogroup A; 99%, Serogroup C; 98%, Serogroup Y; 98%, Serogroup W-135. The seroconversion rates for Menomune – A/C/Y/W-135 recipients were: 100%, Serogroup A; 99%, Serogroup C; 100%, Serogroup Y; 99%, Serogroup W-135.

### ***Immunogenicity in Adults 18 through 55 Years of Age***

Results from the comparative clinical trial conducted in 2554 adults aged 18 through 55 years showed that the immune responses to Menactra and Menomune – A/C/Y/W-135 were similar for all four serogroups.

The percentage of participants with an SBA-BR titer with a  $\geq 4$ -fold rise from the baseline were 81%, Serogroup A; 89%, Serogroup C; 74%, Serogroup Y; and 89%, Serogroup W-135 in the Menactra group and 85%, Serogroup A; 90%, Serogroup C; 79%, Serogroup Y; and 94%, Serogroup W-135 in the Menomune-A/C/Y/W-135 group.

In participants with undetectable pre-vaccination titers (i.e., SBA-BR titers  $< 1:8$  at Day 0), seroconversion rates (defined as the proportions of participants achieving a  $\geq 4$ -fold rise in SBA-BR titers by Day 28) were similar between the Menactra and Menomune – A/C/Y/W-135 recipients. Menactra participants achieved seroconversion rates of: 100%, Serogroup A; 99%, Serogroup C; 91%, Serogroup Y; and 97%, Serogroup W-135. The seroconversion rates for Menomune – A/C/Y/W-135 recipients were: 99%, Serogroup A; 98%, Serogroup C; 97%, Serogroup Y; and 99%, Serogroup W-135.

### **Immunogenicity in Adolescents and Adults Following Booster Vaccination**

For a description of the study design and number of participants, [see **Clinical Trials Experience, Booster Vaccination Study.**] Prior to revaccination, the percentage of participants (n = 781) with an SBA-H titer  $\geq 1:8$  were 64.5%, 44.2%, 38.7%, and 68.5% for Serogroups A, C, Y, and W-135, respectively. Among the subset of trial participants (n = 112) for whom SBA-H responses at Day 6 were assessed, 86.6%, 91.1%, 94.6%, and 92.0% achieved a  $\geq 4$ -fold rise in SBA-H titer for Serogroups A, C, Y, and W-135, respectively. The proportions of participants (n = 781) who achieved a  $\geq 4$ -fold rise in SBA-H titer by Day 28 were 95.0%, 95.3%, 97.1%, and 96% for Serogroups A, C, Y, and W-135, respectively. The proportions of participants who achieved an SBA-H titer  $\geq 1:8$  by Day 28 were  $> 99\%$  for each serogroup.

### **Concomitant Vaccine Administration**

#### ***MMRV (or MMR + V) or PCV7***

In a US, active-controlled trial, 1179 children received Menactra at 9 months and 12 months of age. At 12 months of age, these children received Menactra concomitantly with MMRV (N = 616), or MMR + V (N = 48), or PCV7 (N = 250). Another group of 12-month old children received MMRV + PCV7 (N = 485). Sera were obtained approximately 30 days after the last vaccinations. Measles, mumps, rubella and varicella antibody responses among children who received Menactra and MMRV (or MMR and V) were comparable to corresponding antibody responses among children who received MMRV and PCV7.

When Menactra was given concomitantly with PCV7, the non-inferiority criteria for comparisons of pneumococcal IgG geometric mean concentrations (GMCs) (upper limit of the two-sided 95% CI of the GMC ratio  $\leq 2$ ) were not met for 3 of 7 serotypes (4, 6B, 18C). In a subset of participants with available sera, pneumococcal opsonophagocytic assay GMT data were consistent with IgG GMC data.

### ***Td Vaccine***

In a double-blind, randomized, controlled trial, 1021 participants aged 11 through 17 years received Td vaccine and Menactra concomitantly (N = 509), or Td vaccine followed one month later by Menactra (N = 512). Sera were obtained approximately 28 days after each respective vaccination. The proportions of participants with a 4-fold or greater increase in SBA-BR titer to meningococcal Serogroups C, Y and W-135 were higher when Menactra was given concomitantly with Td vaccine (86% - 96%) than when Menactra was given one month following Td vaccine (65% - 91%). Anti-tetanus and anti-diphtheria antibody responses were similar in both study groups.

### ***Typhim Vi***

In a double-blind, randomized, controlled trial, 945 participants aged 18 through 55 years received Typhim Vi and Menactra concomitantly (N = 469), or Typhim Vi followed one month later by Menactra (N = 476). Sera were obtained approximately 28 days after each respective vaccination. The antibody responses to Menactra and to Typhim Vi components were similar in both study groups.

### **DAPTACEL and IPV**

In a randomized, parallel group, US multi-center clinical trial conducted in children 4 through 6 years of age, Menactra was administered as follows: 30 days after concomitant DTaP (DAPTACEL<sup>®</sup>, Sanofi Pasteur Limited) + IPV (IPOL<sup>®</sup>, Sanofi Pasteur SA) [Group A]; concomitantly with DAPTACEL followed 30 days later by IPV [Group B]; concomitantly with IPV followed 30 days later by DAPTACEL [Group C]. Sera were obtained approximately 30 days after each respective vaccination. [See **Clinical Trials Experience.**]

When Menactra was administered 30 days after DAPTACEL (and IPV) [Group A], significantly lower SBA-H GMTs to all 4 meningococcal serogroups were observed compared to Menactra (and IPV) administered 30 days prior to DAPTACEL [Group C]. When Menactra was administered concomitantly with DAPTACEL [Group B], SBA-H GMTs to meningococcal serogroups A, C, and W-135 were non-inferior to those observed after Menactra (and IPV) [Group C]. The non-inferiority criterion was marginally missed for meningococcal serogroup Y. Non-inferiority of SBA-H GMTs following concomitant administration of Menactra and DAPTACEL compared to those after concomitant Menactra and IPV was concluded if the upper limit of the 2-sided 95% CI of ( $\text{GMT}_{\text{Group C}} / \text{GMT}_{\text{Group B}}$ ) computed separately for each of the serogroups was  $< 2$ .

When Menactra was administered concomitantly with DAPTACEL, antibody responses to three of the pertussis antigens (pertussis toxin, filamentous hemagglutinin, and pertactin) (GMCs), tetanus toxin (% participants with antibody concentrations  $\geq 1.0$  IU/mL), and diphtheria toxin (% participants with antibody concentrations  $\geq 1.0$  IU/mL) were non-inferior to those observed after DAPTACEL and IPV. The pertussis anti-fimbriae GMCs were marginally lower when Menactra and DAPTACEL were administered concomitantly.

## HOW SUPPLIED

Single-dose vial, 0.5 mL. Supplied as a package of 5 vials.

Single-dose vial, 0.5 mL. Supplied as a package of 1 vial.

## STORAGE AND HANDLING

Store at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product that has been exposed to freezing should not be used. Do not use after expiration date.

## PATIENT COUNSELING INFORMATION

Prior to administration of Menactra, the healthcare professional should inform the patient, parent, guardian, or other responsible adult of the potential benefits and risks to the patient [see **ADVERSE REACTIONS** and **WARNINGS AND PRECAUTIONS**]. Patients, parents or guardians should be instructed to report any suspected adverse reactions to their healthcare professional who should report these events to Sanofi Pasteur Inc.

MENACTRA<sup>®</sup> is a registered trademark of Sanofi, its affiliates and subsidiaries.

Product Information as of March 2019.

Manufactured by:

**Sanofi Pasteur Inc.**

Swiftwater PA 18370 USA

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