

AHFS Category 80:12

# Meningococcal Polysaccharide Vaccine Groups A, C, Y and W-135 Combined


 Rx only

## Menomune® – A/C/Y/W-135

*Caution: Federal (USA) law prohibits dispensing without prescription.*

### DESCRIPTION

Menomune® – A/C/Y/W-135, Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined, for subcutaneous use, is a freeze-dried preparation of the group-specific polysaccharide antigens from *Neisseria meningitidis*, Group A, Group C, Group Y and Group W-135. *N. meningitidis* are cultivated with Mueller Hinton agar<sup>1</sup> and Watson Scherp<sup>2</sup> media. The purified polysaccharide is extracted from the *Neisseria meningitidis* cells and separated from the media by procedures which include centrifugation, detergent precipitation, alcohol precipitation, solvent or organic extraction and diafiltration. No preservative is added during manufacture.

The 0.78 mL vial of diluent contains sterile, preservative-free, pyrogen-free distilled water and is used for reconstitution of product supplied in 1 mL vials. The 6 mL vial of diluent contains sterile, pyrogen-free distilled water to which thimerosal (mercury derivative) 1:10,000 is added as a preservative. The 6 mL vial is for reconstitution of product supplied in 10 mL vials. After reconstitution with diluent as indicated on the label, the 0.5 mL dose is formulated to contain 50 µg of “isolated product” from each of Groups A, C, Y and W-135 in an isotonic sodium chloride solution.

Each dose of vaccine is also formulated to contain 2.5 mg to 5 mg of lactose added as a stabilizer.<sup>3</sup> The vaccine when reconstituted is a clear colorless liquid.

Potency is evaluated by measuring the molecular size of each polysaccharide component using a column chromatography method as standardized by the US Food and Drug Administration (FDA) and the World Health Organization (WHO)<sup>4</sup> for Meningococcal Polysaccharide Vaccine.

THIS VACCINE CONFORMS TO THE WORLD HEALTH ORGANIZATION (WHO) REQUIREMENTS.

### CLINICAL PHARMACOLOGY

*N. meningitidis* causes both endemic and epidemic disease, principally meningitis and meningococcemia. As a result of the control of *Haemophilus influenzae* type b infections, *N. meningitidis* has become the leading cause of bacterial meningitis in children and young adults in the United States (US), with an estimated 2,600 cases each year.<sup>5,6</sup> The case-fatality rate is 13% for meningitis disease (defined as the isolation of *N. meningitidis* from cerebrospinal fluid) and 11.5% for persons who have *N. meningitidis* isolated from blood,<sup>5,6</sup> despite therapy with antimicrobial agents (e.g., penicillin) to which US strains remain clinically sensitive.<sup>5</sup>

The incidence of meningococcal disease peaks in late winter to early spring. Based on multistate surveillance conducted during 1989 to 1991, serogroup B organisms accounted for 46% of all cases and serogroup C for 45%; serogroups W-135 and Y and strains that could not be serotyped accounted for most of the remaining cases.<sup>5,6</sup> Recent data indicate that the proportion of cases caused by serogroup Y strains is increasing.<sup>5</sup> In 1995, among the 30 states reporting supplemental data on culture-confirmed cases of meningococcal disease, serogroup Y accounted for 21% of cases.<sup>7</sup> Because of the success of *H. influenzae* type b vaccinations, the median age of persons with bacterial meningitis increased from 15 months in 1986 to 25 years in 1995.<sup>8</sup> The predominate organism causing meningitis in children 2 to 18 years of age is *N. meningitidis* based on 1995 surveillance data.<sup>8</sup> Serogroup A, which rarely causes disease in the US, is the most common cause of epidemics in Africa and Asia. A statewide serogroup B epidemic has been reported in the US.<sup>9</sup> Within the US, a vaccine for serogroup B is not yet available.

Outbreaks of serogroup C meningococcal disease (SCMD) have been occurring more frequently in the US since the early 1990s, and the use of vaccine to control these outbreaks has increased.<sup>5</sup> During 1980-1993, 21 outbreaks of SCMD were identified; eight of these occurred during 1992-1993.<sup>10</sup> Each of these 21 outbreaks involved from three to 45 cases of SCMD, and most outbreaks had attack rates exceeding 10 cases per 100,000 population, which is approximately 20 times higher than rates of endemic SCMD.<sup>5</sup> During 1981-1988, only 7,600 doses of meningococcal vaccine were used to control four outbreaks; whereas, from January 1992 through June 1993, 180,000 doses of vaccine were used in response to eight outbreaks.<sup>5</sup>

Several discoveries impacted the future of meningococcal polysaccharide vaccines and demonstrated the significance of anti-capsular antibodies in protection.<sup>11</sup> In the late 1930s, serogroup-specific antigens of meningococcal serogroups A and C were identified as polysaccharides.<sup>9</sup> During the mid 1940s, investigators demonstrated that the protection of mice by anti-serogroup A meningococcal horse serum was directly related to its content of anti-polysaccharide antibodies.<sup>11</sup> Meningococcal polysaccharide vaccines were first demonstrated to be immunogenic in humans by Gotschlich and his co-workers in the 1960s when immunization of US Army recruits with serogroup A and C polysaccharides induced protective antibodies.<sup>11</sup> The investigators recorded a significantly reduced acquisition rate of serogroup C carriage among vaccinated recruits compared with unvaccinated individuals.<sup>11</sup>

Persons who have certain medical conditions are at increased risk for developing meningococcal infection. Meningococcal disease is particularly common among persons who have component deficiencies in the terminal common complement pathway (C3, C5-C9); many of these persons experience multiple episodes of infection.<sup>5</sup> Asplenic persons also may be at increased risk for acquiring meningococcal disease with particularly severe infections.<sup>5</sup> Persons who have other diseases associated with immunosuppression (e.g., human immunodeficiency virus [HIV] and *Streptococcus pneumoniae*) may be at higher risk for developing meningococcal disease and for disease caused by some other encapsulated bacteria.<sup>5</sup> Evidence suggests that HIV-infected persons are not at substantially increased risk for epidemic serogroup A meningococcal disease;<sup>5</sup> however, such patients may be at increased risk for sporadic meningococcal disease or disease caused by other meningococcal serogroups.<sup>5</sup> Previously, military recruits had high rates of meningococcal disease, particularly serogroup C disease; however, since the initiation of routine vaccination of recruits with bivalent A/C meningococcal vaccine in 1971, the high rates of meningococcal disease caused by those serogroups have decreased substantially and cases occur infrequently.<sup>5</sup>

A retrospective, epidemiological study was conducted in Maryland to compare the incidence of invasive meningococcal infection in college students with that of the general population of the same age. For the years 1992 to 1997, the incidence of meningococcal infection in Maryland college students was similar to the incidence of the general Maryland population of the same age. However, college students residing on-campus appeared to be at higher risk than those residing off campus.<sup>12</sup>

**Vaccine efficacy.** The immunogenicity and clinical efficacy of serogroups A and C meningococcal vaccines have been well established.<sup>5</sup> The serogroup A polysaccharide induces antibody in some children as young as 3 months of age, although a response comparable with that among adults is not achieved until 4 or 5 years of age; the serogroup C component is poorly immunogenic in recipients who are less than 18 to 24 months of age.<sup>5</sup> The serogroups A and C vaccines have demonstrated estimated clinical efficacies of 85% to 100% in older children and adults and are useful in controlling epidemics.<sup>5</sup> Serogroups Y and W-135 polysaccharides are safe and immunogenic in adults and in children greater than 2 years of age.<sup>5</sup> Although clinical protection has not been documented, vaccination with these polysaccharides induces bactericidal antibody. The antibody responses to each of the four polysaccharides in the quadrivalent vaccine are serogroup-specific and independent.<sup>5</sup>

Efficacy of serogroup A meningococcal vaccines was demonstrated in the 1970s in Africa and Finland, Egyptian school children aged 6 to 15 years showed 90% or greater protection during the first year after immunization with two different molecular sizes of serogroup A polysaccharide.<sup>11</sup> The higher molecular weight vaccine provided protection for at least three years.<sup>11</sup> In Finland, a randomized controlled mass immunization trial with serogroup A vaccine was conducted in response to a serogroup A epidemic. Results indicated 90 to 100% protection for three years.<sup>11</sup> In Rwanda, vaccination with bivalent A/C polysaccharide vaccine was performed in response to a serogroup A epidemic. A complete cessation of meningococcal disease was observed within two weeks of vaccination, yet the serogroup A carrier rate remained unchanged.<sup>11</sup>

Efficacy of serogroup C meningococcal vaccines was demonstrated in a field trial involving 20,000 troops in the US Army. Results suggested 90% efficacy under epidemic conditions which existed in basic training centers.<sup>13</sup> In Brazil, young children were vaccinated with serogroup C polysaccharide in response to a serogroup C epidemic. Results indicated that the vaccine was not effective in children under 24 months of age and only 52% effective in children aged 24 to 36 months.<sup>11</sup> However, studies suggested that the vaccine used in this trial was less immunogenic than other batches of similar vaccine that were used in US children; also, it was shown that the molecular size of the vaccine was smaller than the serogroup C polysaccharide in the present vaccine.<sup>13</sup> Thus, it is quite probable that the current serogroup C polysaccharide vaccine is more effective.<sup>11</sup>

A study performed using 4 lots of Menomune<sup>®</sup> – A/C/Y/W-135 in 150 adults showed at least a 4-fold increase in bactericidal antibodies to all groups in greater than 90 percent of the subjects.<sup>14,15</sup>

A study was conducted in 73 children 2 to 12 years of age. Post-immunization sera were not obtained on four children; seroconversion rates were calculated on 69 paired samples. Seroconversion rates as measured by bactericidal antibody were: Group A – 72%, Group C – 58%, Group Y – 90% and Group W-135 – 82%. Seroconversion rates as measured by a 2-fold rise in antibody titers based on Solid Phase Radioimmunoassay were: Group A – 99%, Group C – 99%, Group Y – 97% and Group W-135 – 89%.<sup>16</sup>

**Duration of efficacy.** Measurable levels of antibodies against the group A and C polysaccharides decrease markedly during the first 3 years following a single dose of vaccine.<sup>5</sup> This decrease in antibody occurs more rapidly in infants and young children than in adults. Similarly, although vaccine-induced clinical protection probably persists in schoolchildren and adults for at least 3 years, the efficacy of the group A vaccine in young children may decrease markedly with the passage of time. In a 3-year study, efficacy declined from greater than 90% to less than 10% among children who were less than 4 years of age at the time of vaccination, whereas among children who were greater than or equal to 4 years of age when vaccinated, efficacy was 67% 3 years later.<sup>5,17</sup> In a New Zealand study, children 2 to 13 years of age received a single dose of monovalent group A vaccine, 26% of children 3 to 23 months of age in this study received two doses of the vaccine, given approximately 3 months apart. After 2-1/2 years of active surveillance (1987 to 1989) there were no cases of invasive group A disease in children vaccinated at 2 years of age and older.<sup>18</sup>

## INDICATIONS AND USAGE

Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined, is indicated for active immunization against invasive meningococcal disease caused by these serogroups.<sup>5</sup>

Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined may be used to prevent and control outbreaks of serogroup C meningococcal disease.<sup>5</sup>

For evaluation and management of suspected outbreaks, it is recommended that the health-care workers consult the MMWR for guidance.<sup>5</sup>

Routine vaccination is recommended for the following high-risk groups:<sup>5</sup>

1. Deficiencies in late Complement components (C3, C5-C9).
2. Functional or actual asplenia.
3. Persons with laboratory or industrial exposure to *N. meningitidis* aerosols.
4. Travelers to, and residents of, hyperendemic areas such as sub-Saharan Africa. For information concerning geographic areas for which vaccination is recommended, contact CDC at 404-332-4559.

The American College Health Association (ACHA) also recommends that college students consider vaccination to reduce the risk for potentially fatal meningococcal disease.<sup>19</sup>

Vaccinations also should be considered for household or institutional contacts of persons with meningococcal disease and for medical and laboratory personnel at risk of exposure to meningococcal disease.

This vaccine will not stimulate protection against infections caused by organisms other than Groups A, C, Y and W-135 meningococci.

Protective antibody levels may be achieved within 7 to 10 days after vaccination.<sup>5</sup>

Menomune® – A/C/Y/W-135 vaccine is not to be used for treatment of actual infection.

Menomune® – A/C/Y/W-135 vaccine will not protect against other etiologic agents, including *N. meningitidis* serogroup B, that cause meningitis.

Menomune® – A/C/Y/W-135 vaccine is not indicated for infants and children younger than 2 years of age except as short-term protection of infants 3 months and older against Group A.<sup>11</sup>

*As with any vaccine, vaccination with Menomune® – A/C/Y/W-135 may not protect 100% of susceptible individuals.*

For persons remaining at high-risk, especially children who were first vaccinated at < 4 years of age, revaccination may be indicated.<sup>5</sup> (See **DOSAGE AND ADMINISTRATION** section.)

### **CONTRAINDICATIONS**

Immunization should be deferred during the course of any acute illness.

IT IS A CONTRAINDICATION TO ADMINISTER MENOMUNE® – A/C/Y/W-135 TO INDIVIDUALS KNOWN TO BE SENSITIVE TO THIMEROSAL OR ANY OTHER COMPONENT OF THE VACCINE. FOR INDIVIDUALS SENSITIVE TO THIMEROSAL, ADMINISTER THE ONE DOSE PACKAGE SIZE AND RECONSTITUTE WITH THE 0.78 ML VIAL OF DILUENT THAT CONTAINS NO PRESERVATIVE.

### **WARNING**

**This product contains dry natural latex rubber as follows:** The stopper to the vial contains dry natural latex rubber.

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

Menomune® – A/C/Y/W-135 should NOT be given at the same time as whole-cell pertussis or whole-cell typhoid vaccines due to combined endotoxin content.<sup>20,21</sup>

### **PRECAUTIONS**

#### **GENERAL**

Care is to be taken by the health-care provider for the safe and effective use of Menomune® – A/C/Y/W-135.

#### **EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE TO COMBAT UNEXPECTED ANAPHYLACTIC OR OTHER ALLERGIC REACTIONS.**

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible sensitivity to the vaccine or similar vaccines and to possible sensitivity to dry natural latex rubber.

*Special care should be taken to avoid injecting the vaccine intradermally, intramuscularly, or intravenously since clinical studies have not been done to establish safety and efficacy of the vaccine using these routes of administration.*

Health-care providers should obtain the previous immunization history of the vaccinee, and inquire about the current health status of the vaccinee.

A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of hepatitis and other infectious agents from person to person. Needles should not be recapped and should be disposed of according to biohazard waste guidelines.

#### **INFORMATION FOR PATIENT**

Patients, parents or guardians should be fully informed of the benefits and risks of immunization with Menomune® – A/C/Y/W-135.

Patients, parents or guardians should be instructed to report any serious adverse reactions to their health-care provider.

As part of the patient's immunization record, the date, lot number and manufacturer of the vaccine administered should be recorded.<sup>22,23,24</sup>

#### **DRUG INTERACTIONS**

If Menomune® – A/C/Y/W-135 is administered to immunosuppressed persons or persons receiving immunosuppressive therapy, an adequate immunologic response may not be obtained.

#### **CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY**

Menomune® – A/C/Y/W-135 has not been evaluated in animals for its carcinogenic, mutagenic potentials or impairment of fertility.

#### **PREGNANCY**

##### **REPRODUCTIVE STUDIES – PREGNANCY CATEGORY C**

Animal reproduction studies have not been conducted with Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135. It is also not known whether Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 should be given to a pregnant woman only if clearly needed.

Although there is limited data, studies to date have found no evidence of teratogenicity of the polysaccharide quadrivalent meningococcal vaccine when given to pregnant women.<sup>25</sup>

#### NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Menomune® – A/C/Y/W-135 is administered to a nursing woman.

#### PEDIATRIC USE

**SAFETY AND EFFECTIVENESS OF MENOMUNE® – A/C/Y/W-135 IN CHILDREN BELOW THE AGE OF 2 YEARS HAVE NOT BEEN ESTABLISHED.**

#### ADVERSE REACTIONS

Adverse reactions to meningococcal vaccine are mild and consist principally of pain and redness at the injection site for 1 to 2 days. Pain at the site of injection is the most commonly reported adverse reaction, and a transient fever might develop in less than or equal to 2% of young children.<sup>5</sup>

Adverse events reported by 150 adults following vaccination with Menomune® – A/C/Y/W-135 are shown in Table 1.<sup>14</sup> The subjects were observed for three weeks following vaccination. Local reactions resolved within 48 hours and no significant systemic reactions were reported.<sup>14</sup>

**TABLE 1<sup>14</sup> ADVERSE EVENTS (%) FOLLOWING VACCINATION OF 150 ADULTS WITH MENOMUNE® – A/C/Y/W-135**

REACTIONS	MILD	MODERATE
<b>Local</b>		
Pain	2.6	2.0
Tenderness	36.0	9.0
Diameter	< 2 in.	≥ 2 in.
Erythema	3.8	1.2
Induration	4.4	1.2
<b>Systemic</b>		
Headaches	5.2	1.8
Malaise	2.5	0
Chills	2.5	0
Oral Temperature (°F)	2.6 (100–101)	0.6 (> 101)

In a clinical study involving 73 children 2 to 12 years of age, who received Menomune® – A/C/Y/W-135, local reactions consisting of erythema or tenderness were seen in approximately 40% of the children.<sup>15</sup> In another clinical study involving 53 children 4 to 6 years of age, who received Menomune® – A/C/Y/W-135, erythema was seen in 89% of the children, swelling in 92% and tenderness in 64%. None of these reactions were considered serious or necessitated medical intervention.<sup>26</sup>

On rare occasions, IgA nephropathy has occurred following vaccinations with Menomune® – A/C/Y/W-135. However, a cause and effect relationship has not been established.<sup>16</sup>

Menomune® – A/C/Y/W-135 should NOT be given at the same time as whole-cell pertussis or whole-cell typhoid vaccines due to combined endotoxin content.<sup>20,21</sup>

As with the administration of any vaccine, vaccine components can cause hypersensitivity reactions in some recipients.

#### Reporting of Adverse Events

The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records and to report occurrences of certain adverse events to the US Department of Health and Human Services. Reportable events include those listed in the Act for each vaccine and events specified in the package insert as contraindications to further doses of that vaccine.<sup>22,23,24</sup>

Reporting by patients, parents or guardians of all adverse events occurring after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by the health-care provider to the US Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting Systems (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967.<sup>24</sup>

**Health-care providers also should report these events to the Director of Scientific and Medical Affairs, Aventis Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463.**

#### DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If either of these conditions exist, the vaccine should not be administered.

Reconstitute the vaccine using only the diluent supplied for this purpose. Draw the volume of diluent shown on the diluent label into a suitable size syringe and inject into the vial containing the vaccine. Shake vial until the vaccine is dissolved.

The immunizing dose is a single injection of 0.5 mL administered **subcutaneously**.

*Special care should be taken to avoid injecting the vaccine intradermally, intramuscularly, or intravenously since clinical studies have not been done to establish safety and efficacy of the vaccine using these routes of administration.*

### Primary Immunization

For both adults and children, vaccine is administered subcutaneously as a single 0.5 mL dose. Protective antibody levels may be achieved within 7 to 10 days after vaccination.<sup>5</sup>

### REVACCINATION

Revaccination of a single 0.5 mL dose administered subcutaneously may be indicated for individuals at high-risk of infection, particularly children who were first vaccinated when they were less than 4 years of age; such children should be considered for revaccination after 2 or 3 years if they remain at high-risk. Although the need for revaccination in older children and adults has not been determined, antibody levels decline rapidly over 2 to 3 years, and if indications still exist for immunization, revaccination may be considered within 3 to 5 years.<sup>5,18</sup>

Simultaneous administration of Menomune<sup>®</sup> – A/C/Y/W-135 can be given concurrently with other vaccines at separate sites and separate syringes.<sup>27</sup> However, due to the combined endotoxin content, the vaccine should NOT be administered at the same time as whole-cell pertussis or whole-cell typhoid vaccines.<sup>20,21</sup> (See **WARNINGS** section.)

### HOW SUPPLIED

Vial, 1 Dose, with 0.78 mL vial of diluent (contains NO preservative). Product No. 49281-489-01

Vial, 1 Dose (5 per package) with 0.78 mL vial of diluent (5 per package) (contains NO preservative). Product No. 49281-489-05

Vial, 10 Dose, with 6 mL vial of diluent (contains preservative) for administration with needle and syringe (NOT to be used with jet injector). Product No. 49281-489-91

### STORAGE

Store freeze-dried vaccine and reconstituted vaccine, when not in use, between 2° – 8°C (35° – 46°F). Discard remainder of multidose vials of vaccine within 10 days after reconstitution. The single dose vial should be used within 30 minutes after reconstitution.

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