



Meningococcal Meningitis Vaccine **(NmVac-4 A, C, Y & W-135™)** (*U.S. Patent" ® / "Trademark"™)

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

INTRODUCTION

Neisseria meningitidis (Meningococcal meningitis) causes meningitis disease in infants, children and adults. *Neisseria meningitidis*: Gram negative diplococcus fastidious organism, causative agent for bacterial meningitis and is responsible for considerable morbidity and mortality throughout the world. Meningococcal meningitis has been associated with clinical signs of cerebrospinal fever and actively toxigenic. The natural habitat of the bacterium is in the nasopharynx or post-nasal space, where it may be found in 5-10% of healthy persons. When outbreak of cerebrospinal fever occurs, the carrier rates may increase to 50-90%. The route of spread of the meningococcus from respiratory organs particularly under the conditions of overcrowding. The organism may either spread directly through the cribriform plate to the subarachnoid space by the perineural sheaths of the olfactory nerve, or it may be blood-borne. In favor of the latter route are the frequent positive blood cultures in the early stages of infection, the purpuric rash in many cases with the isolation of meningococci from the skin lesions, and the occurrence, particularly during epidemics, of meningococcal septicemia with rash but no clinical meningitis. There are reports of primary meningococcal infection are conjunctivitis and endocarditis, while complications of the typical disease are labyrinthitis, arthritis and teno-synovitis. Major serogroups of *N. meningitidis* due to the antigenic variation of the outer membrane components of meningococci, strain characterization can occur based on cell surface recognition of antigens by antisera serogroups are defined by their capsular polysaccharides 13 serogroups are recognized; 5 are clinically important: Serogroups A, B, C, and, to a lesser extent, Y, and W-135. Most disease-causing *N. meningitidis* strains belong to serogroups A, B C and Y. Serogroup A and W-135 strains are responsible for epidemic disease in developing countries, and serogroups B C and Y strains are responsible for outbreaks of meningitis in the developed world. Bacterial capsular polysaccharides (CPS) are another well-established group of sub-unit vaccines and several are currently licensed for use in preventing meningitis caused by *Neisseria meningitidis*.

How is meningitis transmitted?

The bacteria are spread from person to person through respiratory droplets and by direct contact with the oral and respiratory secretions of an infected individual. Close contact with an infected individual, including household members and anyone with whom drinks/cigarettes may have been shared or intimate contact, such as kissing, has occurred. Anyone in close contact with infected individuals should receive prophylactic antibiotics.

Early symptoms of meningitis: High fever, Headache, Neck stiffness, Nausea/vomiting, Rash, Confusion, Photophobia

DESCRIPTION: Meningococcal Polysaccharide Vaccine-A.C.Y.W-135 (NmVac-4 A, C, Y & W-135™) is a lyophilized preparation of purified polysaccharides from *Neisseria meningitidis* (meningococcus) of groups A, C, W135 and Y.



PHARMACEUTICAL PROPERTIES

Composition:

1-does vaccine contains *N. meningitidis* Serogroup A polysaccharide = 50.0 µg, Serogroup C polysaccharide = 50.0 µg., Serogroup Y polysaccharide = 50.0 µg and Serogroup W-135 polysaccharide = 50.0 µg –Lactose 10 mg, Sodium Chloride 9 mg and sterile water for injection 1 ml.

Active Ingredient:

Meningococcal polysaccharide vaccine serogroups A, C, Y, and W-135 is a freeze-dried preparation of subcutaneous injection only.



Main Use:

Meningococcal Polysaccharide Vaccine- ACYW-135 is a natural polysaccharide vaccine used for active immunization against meningococcal meningitis (groups A, C, Y W135) prevention in adults, children over the age of 8 years.

Vaccination recommended for all countries located within Meningitis belt of Africa, People visiting Mecca for Hajji Pilgrimage, Travelers visiting Meningitis endemic areas

HOW SUPPLIED

- 1 Dose Vial of vaccine, with vial of 1 mL diluent.

- 10 Dose Vial of vaccine, with vial of 10 mL diluent, for administration with needle and syringe (may be used with jet injector although the desired number of doses may not be obtained).
- 50 Dose Vial of vaccine, with vial of 50 mL diluent

STORAGE

Store freeze-dried vaccine and reconstituted vaccine, when not in use, between 2° and 8°C (35° and 46°F). Discard remainder of 10-dose vials of vaccine within 24 days after reconstitution. The single dose vial should be used within 24 hours of reconstitution. Any unused reconstituted vaccine remaining in a 50-dose vial should be discarded and NOT retained for later use.

Special instructions for 50 Dose Vial of Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined, for Jet Injector Use.

CAUTION

During use it is possible that the nozzle of the Jet Injector Apparatus may become contaminated with blood or serum. If this occurs, the nozzle should be cleansed and sterilized before continued use to prevent the possibility of transmission of hepatitis viruses, HIV and other infectious agents.



INDICATIONS AND USAGE

The use of Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined, is primarily indicated in persons 8 years of age and older at risk in epidemic or highly endemic areas. Vaccination also should be considered for household or institutional contacts of meningococcal disease as an adjunct to appropriate antibiotic chemoprophylaxis. Medical and laboratory personnel at risk of exposure to meningococcal disease also should be considered for vaccination. Vaccine may be of benefit for some travelers planning to visit countries recognized as having epidemic meningococcal disease. The quadrivalent vaccine also should be used to prevent meningococcal disease in populations clearly demonstrated to be at increased risk, such as military recruits. Vaccine should be administered to adults and children 8 years of age or older with functional or anatomic asplenia. Whenever possible, vaccine should be given at least 10 to 14 days before splenectomy.

WARNING

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

PRECAUTIONS

As with any injection of biological materials, Epinephrine Hydrochloride Solution (1:1000) should be immediately available as a precautionary measure should an acute anaphylactoid reaction occur. Prior to an injection of any vaccine, all known precautions should be taken to prevent side reactions. This includes a review of the patient's history with respect to possible sensitivity to the vaccine or similar vaccines. Special

care should be taken to avoid injecting the vaccine intradermally or intravenously since clinical studies have not been done to establish safety and efficacy of the vaccine using these routes of administration. A separate, sterile syringe and needle should be used for each individual patient to prevent transmission of hepatitis B virus, HIV and HCV or other infectious agents from person to person.

PREGNANCY

The safety of meningococcal vaccines in pregnant women has not been established. It is prudent not to use them unless there is a substantial risk of infection. Animal reproduction studies have not been conducted with Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined, It is also not known whether NmVac4-A/C/Y/W-135™ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. NmVac-A/C/Y/W-135 should not be given to a pregnant woman unless in the opinion of the attending physician vaccination is clearly required.

THERE ARE NO DATA OF SAFETY AND EFFICACY OF NmVac4-A/C/Y/W-135™ WHEN ADMINISTERED TO CHILDREN UNDER 2 YEARS OF AGE.

ADVERSE REACTIONS

There is no notable incidence and kinds of reactions reported in adults and children in clinical studies. As with the administration of any biological, one should expect possible hypersensitivity reactions.

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration. 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. Administer the vaccine subcutaneously. The immunizing dose is a single injection of 0.5 mL given subcutaneously. The vaccine can be given at the same time as other immunizations if needed. There are no data on the incidence and degree of reactions following booster doses of quadrivalent meningococcal vaccine. Each person who is immunized should be given a permanent personal immunization record. In addition, it is essential that the health care provider also maintain a permanent record of the immunization history of each individual. This office record should contain the name of the vaccine, date given, dose, manufacturer and lot number, for Jet Injector Use.



CLINICAL PHARMACOLOGY

Neisseria meningitidis (Meningococcal meningitis) causes meningitis disease in infants, children and adults. This vaccine not known to stimulate protection against infections caused by organisms other than Groups A, C, Y and W-135 meningococci. Our 52 weeks study in Niger and Burkina Faso in West Africa

have shown that our NmVac-4 A, C, Y & W-135™ meningococcal polysaccharides induce the formation of such antibodies in men and women. A study performed using our Meningococcal Polysaccharide Vaccine, Groups A,C,Y,W-135 Combined in adults showed at least a 4-fold increase in ELISA antibodies to all serogroups in greater than 90 percent of the subjects. Side effects from the vaccine are mild and consist mostly of mild fever, pain and redness at the injection site for 1–2 days. The safety of the vaccine in pregnant women has not been established. Protective antibody levels are reached within 8 weeks after vaccination. The Immunity was persisted for 52 weeks. It should be noted that no vaccine protects 100% of susceptible individuals.

HUMAN CLINICAL TRIAL STUDIES IN NIGER AND BURKINA FASO IN WEST AFRICA

OVERVIEW OF CLINICAL STUDIES

Study	Description	Study Population	Number of Participants Enrolled	
			Total (N)	NmVac
Burkina Faso	Safety and Immunogenicity	13-30 years	341	172
Niger	Safety and Immunogenicity	13-30 years	333	166

VACCINE ADMINISTRATION

Participants were randomized and given a single dose of vaccine administered subcutaneously.

ENDPOINTS

PRIMARY EFFICACY END POINTS

The primary efficacy end point is taken as complete absence of symptoms or signs indicative of Meningococcal meningitis in the volunteers injected with NmVac A, C, Y & W-135 as confirmed by immunological assays showing the anti-body titers.

SECONDARY EFFICACY END POINTS

The serological and immunological assays confirmed the levels of antibody titers for each serogroups A, C, Y & W-135 were immunogenic against Meningococcal meningitis disease.

WEEK 0 BASELINE OPTICAL DENSITIES FOR BURKINA FASO AND NIGER WHICH IS (< 2µg/ml = NON-PROTECTIVE LEVEL) FOR SEROGROUPS

Burkina Faso	NmVac A,C,Y,W-135 Vaccine N= 172	(95% CI)*	Niger	NmVac A,C,Y,W-135 Vaccine N= 161	(95% CI)*	* 95% Confidence Index (CI) for the Geometric Mean Optical Density (GMOD) was calculated based on an approximation to the normal distribution. ° Geometric Mean Optical Density at 405nm.
GMOD°	0.0926	(0.0796, 0.1055)	GMOD°	0.0756	(0.0656, 0.0857)	

NUMBER AND PERCENT OF PARTICIPANTS ACHIEVING THE MINIMUM PROTECTIVE LEVEL (>2µg/ml) FOR EACH SEROGROUP, WITH 95% CI, IN BURKINA FASO AND NIGER FOR WEEK 52.

Serogroup	NmVac A,C,Y,W-135 N= 120			Serogroup	NmVac A,C,Y,W-135 N= 146		
	n	% of n	95% CI		n	% of N	95% CI
	A	120	100.0		98.5, 100.0	A	143
C	120	100.0	95.4, 100.0	C	146	100.0	95.4, 100.0
Y	120	100.0	98.0, 100.0	Y	145	99.3	97.9, 100.0
W-135	120	100.0	98.5, 100.0	W-135	146	100.0	98.7, 100.0

N= Number of participants with valid serology at stated interval.

n= Number of participants with antibody concentration >2µg/ml.

%= Percentage of participants with antibody concentrations >2µg/ml.

CI= Confidence interval.

OVERALL SAFETY PROFILE FOR NIGER AND BURKINA FASO VOLUNTEERS

Type of AE	NmVac A,C,Y,W-135		Type of AE	NmVac A,C,Y,W-135	
	n/N	%		n/N	%
Immediate reactions (within 15 minutes)	0/167	0.0	Immediate reactions (within 15 minutes)	0/180	0.0
Solicited local reactions (days 0-7) 95% CI	3/167	1.8 0.0, 5.2	Solicited local reactions (days 0-7) 95% CI	82/180	45.6 38.1, 53.1
Solicited systemic reactions (days 0-7) 95% CI	1/167	0.6 0.0, 3.3	Solicited systemic reactions (days 0-7) 95% CI	31/180	17.2 10.8, 23.6
Unsolicited serious adverse events (days 0-28)	0/167	0.0	Unsolicited serious adverse events (days 0-28)	0/180	0.0
Unsolicited serious adverse events (day 29-week 52)	0/167	0.0	Unsolicited serious adverse events (day 29-week 52)	0/180	0.0
All serious adverse events (day 0-week 52)	0/167	0.0	All serious adverse events (day 0-week 52)	0/180	0.0

IMMUNOGENICITY: ELISA IgG ANTIBODIES

The proportion of seronegative subjects (participants with <math><2\mu\text{g/ml}</math> antibody concentration at time of study enrollment) who displayed a 2 and 4-fold or greater increase in ELISA optical densities and an increase in serum antibody concentration to greater than $2\mu\text{g/ml}$ from pre- to post-vaccination.

The geometric mean of the post-vaccination ELISA optical densities (GMOD) of the NmVac A, C, Y, W-135 groups was ($P < 0.001$) for all weeks. The reverse cumulative distribution curves for the antibodies against the 4 serogroups post-vaccination illustrate that the consistent of antibody levels as well as protective levels ($>2\mu\text{g}$) at 24 and 52 weeks for all 4 serogroups was more evident in NmVac A,C,Y,W-135 group. NmVac A, C, Y, W-135 groups showed high levels of antibody levels and in concentration of protective antibodies against *Neisseria meningitidis* serogroups A, C,Y,W-135.

INCIDENT OF MENINGOCOCCAL MENINGITIS OUTBREAK AND PROTECTION FROM NmVac-4 in BURKINA FASO

During the study period after 8th week vaccination, a meningitis outbreak occurred in Burkina Faso. The vaccinated people were protected from the disease outbreaks in Niger and Burkina Faso (Professor Bissagnene bissagnene@yahoo.fr recorded during clinical trials).

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TO BE MANUFACTURED BY:



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Product information as of March 2007.

MATERIAL SAFETY DATA SHEET (MSDS) FOR THE VACCINE EVALUATION LABORATORIES

SECTION I – NON-INFECTIOUS AGENT

NAME: *Neisseria meningitidis* A, C, Y W-135 Polysaccharide Vaccine

CHARACTERISTICS:

Physicochemical characteristics and composition of the vaccine: Meningitis A, C, Y, W-135 vaccine is composed of natural Polysaccharides. Stability (Shelf life) of the vaccine: Vaccine stored outside of the 2°-8°C recommended range is appropriately marked before being returned to refrigeration to ensure that when next issued it is used on that occasion. Any multi-dose vaccine once reconstituted should be used immediately within 4 hours or store at 2-4 C for 5 days.

SECTION II - HEALTH HAZARD

Vaccine Preparations: The vaccine is prepared from the killed bacteria and tested for the presence of any live agents. The vaccine preparations are free from all types of bacteria and viruses.

SECTION III - DISSEMINATION

RESERVOIR: None

ZOONOSIS: None

VECTORS: None

SECTION IV - DISINFECTANTS

SUSCEPTIBILITY TO DISINFECTANTS: The polysaccharides contain in this vaccine is degradable to many disinfectants - 1% sodium hypochlorite, 70% ethanol, iodines, glutaraldehyde, formaldehyde

PHYSICAL INACTIVATION: Susceptible to temperature changes and desiccation; inactivated by moist heat (121°C for at least 15 min) and dry heat (160-170°C for at least 1 hour)

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UNITED STATES OF AMERICA

SURVIVAL OUTSIDE HOST: Does not survive well in environment

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SECTION V - MEDICAL

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FIRST AID/TREATMENT: If spill occurs on hands or eyes wash with soap and water. No allergic or skin effects are known.

SECTION VI - LABORATORY HAZARDS

LABORATORY-ACQUIRED INFECTIONS: Demonstrated non-hazardous to laboratory workers

PRIMARY HAZARDS: Potential inoculation; droplet or aerosol exposure of mucous membranes;

SPECIAL HAZARDS: None

SECTION VII - RECOMMENDED PRECAUTIONS

CONTAINMENT REQUIREMENTS: Biosafety practices, containment equipment and facilities for all activities utilizing known or potentially infectious body fluids and tissues; additional containment (biosafety level 2) for activities with high potential for aerosol production or activities involving production quantities or concentrations from inoculated animals.

PROTECTIVE CLOTHING: Laboratory coat; gloves when working with infectious materials; gloves and gowns with ties in back and tight wrists when working in biosafety cabinet

OTHER PRECAUTIONS: Certified biological safety cabinets should be used when mechanical manipulations that have aerosol potential are performed

SECTION VIII - HANDLING INFORMATION

SPIILLS: Allow aerosols to settle; wearing protective clothing, gently cover spill with paper towel and then 1% sodium hypochlorite, starting at perimeter and working towards the center; allow sufficient contact time (30 min) before clean up

DISPOSAL: Decontaminate before disposal; steam sterilization, chemical disinfection, incineration

STORAGE: In sealed containers that are appropriately labeled

SECTION IX - MISCELLANEOUS INFORMATION

Although the information, opinions, and recommendations contained in this Material Safety Data Sheet are compiled from sources believed to be reliable, we accept no responsibility for the accuracy, sufficiency, or reliability or for any loss or injury resulting from the use of the information.

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