وفقا لقرار اللجنة الدائمة للمستحضرات الحيوية بسري أعضاء اللجنة العلمية الدائمة لقرارات الدم بجلسة يوم الثلاثاء ٢١/١٠/٢٠٢٠م

Instructions for Group A and C Meningococcal Polysaccharide Vaccine

Please read the instructions carefully and follow physician' s guidance to use

【Name】

Generic name: Group A and C Meningococcal Polysaccharide Vaccine
English name: Group A and C Meningococcal Polysaccharide Vaccine

【Constituents and Characters】

This vaccine is made by mixture of group A and C Neisseria meningitides capsular polysaccharide antigens, which are extracted and purified through the cultures of Neisseria meningitides group A and C, respectively, with lactose as stabilizer for final lyophilization. The finished product is white and loose cake, can be easily dissolved with diluent (sterile water for injection) to be clear liquid.

Active Ingredients: Group A and C meningococcal polysaccharide
Other Composition: Lactose, Sodium Chloride
Diluent: Sterile water for injection

【Eligibles】

For 2 years old of age and older.

【Action and Use】

The vaccine can induce humoral immune response in recipients following immunization. It is used to prevent epidemic cerebrospinal meningitis caused by group A and C Neisseria meningitides.

【Presentation】

After reconstitution, it shall be 0.5ml per vial. Each single human dose is 0.5 ml containing 50μg of group A and group C meningococcal polysaccharide, respectively.

【Administration Schedule and Dosage】

(1) Reconstitute the vaccine with the accompanying diluent according to indicated amount. With gentle shaking the dried cake is easily dissolved. After reconstitution the vaccine should be used immediately.
(2) The vaccine shall be injected subcutaneously into lateral upper arm.
(3) A single dose of 0.5ml should be administered only once for each human.
Immunization shall be completed before the epidemic season of cerebrospinal meningitis.

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٢٢/٨/٢٠٢٤

【Adverse Reactions】

Common adverse reactions:
(1) The vaccine may cause pain, tenderness, mild or moderate swelling, inflammatory cell infiltration at the injection site within 24 hours of vaccination. In most cases, they spontaneously resolve within two to three days without further medical attention.
(2) Transient fever may occur after vaccination, most of which are mild, can be relieved spontaneously after 1-2 days without further medical attention. Symptomatic treatment can be given to those with moderate fever or fever lasting for more than 48 hours.

Rare adverse reactions:
(1) Severe fever reaction: Symptomatic treatment shall be given to prevent febrile convulsion.
(2) Severe redness or swelling at the injection site or other complications: Symptomatic treatment shall be given.

Extremely rare adverse reactions:
(1) Anaphylactic rash: Rash may occur with 72 hours after vaccination. Once occurred, timely antianaphylactic treatment shall be given.
(2) Anaphylactic shock: Anaphylactic shock may occur within one hour after vaccination. Emergency treatment including injection with adrenaline shall be given promptly.
(3) Allergic purpura: Antianaphylactic treatment with corticosteroid should be given. If the treatment is inappropriate or delayed, purpura nephritis may be complicated.
(4) Angioneurotic edema and allergic neuritis may occur occasionally.
(5) Allergic exfoliative dermatitis cases have been reported occasionally.

【Contraindications】

(1) Individuals with known allergic reactions to any component of the vaccine.
(2) Individuals with acute diseases, severe chronic diseases, fever or during acute attack of chronic diseases.
(3) Individuals with encephalopathy, uncontrolled epilepsy, or other progressive neurological diseases.

【Precautions】

(1) The vaccine should be used with caution to individuals with: family or individual convulsion history, chronic diseases, history of epilepsy, allergic constitution or nursing women.
(2) Do not use the vaccine if the container shows abnormalities, such as crack, illegible label and turbidity after reconstitution.
(3) Adrenaline should be available for first aid in case of severe anaphylactic reactions. The recipients shall be observed for at least 30 minutes on site after injection.
(4) Should not be frozen.

【Storage】

Store and ship at 2- 8℃, protected from light.

【Packaging】

1 ml vial. Each vial of lyophilized vaccine is accompanied with one vial of 0.5ml diluent.

【Shelf Life】

The shelf life is 24 months. The expiry date of the vaccine is indicated on the label and packaging.

WALVAX®
YUXI WALVAX BIOTECHNOLOGY CO., LTD.

【Manufacturer】

Enterprise : Yuxi Walvax Biotechnology Co., Ltd.
Address: No. 83 South Dongfeng Road, High-tech Zone, Yuxi, Yunnan Province, China
Zip code: 653100
Tel: +86-877-2076210
Fax: +86-877-2076918
Website: http://www.walvax.com

【Imported by】

Egyptian Company For Production of Vaccines, Sera and Drugs
Egyvac, One of Affiliated Companies of VACSERA
51 Wezaret EL Zeraa ST., Agouza, Giza, Egypt
Tel: (+202)37611111 - **Fax:** (+202)37483187
Website: www.vacsera.com

【Revision Date】

September 15, 2023

To report any side effect(s):

- Egyptian Pharmacovigilance Centre (EPVC):
Address: 21 AbdelAziz Al Saoud St., Manial ElRawda, Giza, Egypt.
e-mail for reporting: pv.followup@edaegypt.gov.eg
Website for reporting: www.edaegypt.gov.eg
Hotline: 15301
Scan QR code:

طبقاً لقرار اللجنة العلمية المتخصصة للمستحضرات البيولوجية بدعوة أعضاء اللجنة - العلمية المتخصصة لأمراض الدم بجلسة افتراضية يوم الثلاثاء ٢٠٢١/١٠/٢٦م

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF VACCINE

Product name: Group A and C Meningococcal Polysaccharide Vaccine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The vaccine is supplied as a single dose vial of lyophilized powder, with corresponding single dose vial of diluent. After reconstitution, each dose (0.5 mL) of vaccine contains:

Active Substances	Quantity
Neisseria meningitidis group A polysaccharide	50 μg
Neisseria meningitidis group C polysaccharide	50 μg
Excipients	Quantity
Lactose	4 mg
Sodium chloride	4.25 mg

3 PHARMACEUTICAL FORM

Lyophilized powder for injection, with 0.5 mL sterile water for injection as diluent per dose.

The freeze-dried product looks like a white crisp cake. After reconstitution with diluent as the stated value, it shall immediately turn into a clear solution free of foreign matters.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Group A and C Meningococcal Polysaccharide Vaccine is indicated for active immunization to prevent invasive meningococcal diseases caused by *Neisseria meningitidis (N. meningitidis)* serogroups A and C. Humoral immune response can be elicited after immunization.

The vaccine does not protect against diseases caused by *N. meningitidis* serogroups that are not contained in the vaccine.

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سيار محمود عبد الفاطي
تاريخ ٢٠٢٤/٨/٢٦

4.2 Posology and Method of Administration

Posology

Individuals 2 years of age and older

According to indicated amount, the vaccine should be reconstituted with the accompanying diluent with gentle shaking. After reconstitution the vaccine should be used immediately and be injected subcutaneously into lateral upper arm. It must not be administered intravascularly or intradermal. A single dose of 0.5 mL should be administered only once for each human. Immunization shall be completed before the epidemic season of cerebrospinal meningitis.

Individuals less than 2 years of age

The safety and efficacy of this vaccine in children aged less than 2 years of age have not yet been established. Limited data are available.

Elderly population

The safety and efficacy of this vaccine in individuals ≥ 60 years of age have not yet been established. Limited data are available.

4.3 Contraindications

Do not use the vaccine under any of the following circumstances:

(1) Individuals with known allergic reactions to any components of the vaccine.

(2) Individuals with acute diseases, severe chronic diseases, fever or during acute attack of chronic diseases.

(3) Individuals with encephalopathy, uncontrolled epilepsy, or other progressive neurological diseases.

(4) Individuals with renal disease, heart disease and active tuberculosis.

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

As with other vaccines, this vaccine should be postponed in individuals suffering from an acute severe febrile illness. The presence of a minor infection is not a contraindication.

4.4 Precautions

(1) Drugs such as epinephrine must always be readily available in case of a rare anaphylactic event following administration of the vaccine. The person should be observed on-site for at least 30 minutes after the injection.

(2) Do not vaccinate via intravenous route or by gluteal intramuscular injection, and ensure the syringe needle is not puncturing blood vessels during inoculation since the clinical safety, and efficacy of those three routes have not been confirmed.

(3) Do not use the vaccine in case that any crack is observed in the container, loosened stopper, detached label, foreign particle(s) or discoloring inside the container, etc. Do not use the vaccine after the expiration date.

(4) The vaccine should be used with caution to individuals with: family or individual convulsion history, chronic diseases, history of epilepsy, allergic constitution or nursing women.

(5) Strictly prevented from freezing.

4.5 Interaction with other Medicinal Products and other Forms of Interaction

(1) No clinical data of this product co-administrated with other vaccines are currently available.

(2) Any medications, being or have recently been administered, including OTCs, should be reported to the physician.

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إدارة تسجيل المستحضرات الحيوية
نشرة معتمدة: ميار محمد عبد العال
تاريخ: ٢٠٢٤/٨/٢٥

4.6 Fertility, Pregnancy and Lactation

Fertility

No data are currently available for fertility in humans.

Pregnancy

No data are currently available for using the product in pregnant women. The potential risk for pregnant women is unknown.

Lactation

It is unknown whether MPV AC is excreted into human milk. MPV AC should only be used during breast-feeding when the possible advantages outweigh the potential risks.

4.7 Effects on Ability to Drive and Use Machines

Studies of the effect on the ability to drive and use machines have not been conducted. However, when considering this issue, the possible side effects of MPV AC and the clinical status of the patient should be taken into account.

4.8 Adverse Reactions

4.8.1 Clinical Trials

4.8.1.1 Phase I Clinical Trial

A phase I clinical trial of the vaccine (MPV AC) was conducted in China, including 60 subjects (above 2 years of age), of which administrated with single dose (0.5 mL) of MPV AC. All subjects were observed for 30 minutes after immunization at the investigation site, and the investigator actively collected the systemic and local reactions at 6, 24, 48 and 72 hours after vaccination, and the adverse events/reactions were reported by the subjects or collected by regular follow-up 7 days after immunization.

Incidence Rates and Severity of Solicited Adverse Reactions

A total of 3 subjects experienced systemic adverse reactions, of which the fever and rash.

A total of 1 subject experienced local adverse reactions, of which the pain at injection site.

The 1 of fever is mild reaction, and 1 fever and 1 pain at injection site are moderate reactions. No severe reaction was observed in this trial.

The adverse reactions after inoculating the vaccine in domestic clinical trials with 60 subjects (including toddlers, children and adults) are as follows.

Table 4-1 Adverse Reactions after Vaccination of Group A and C Meningococcal Polysaccharide Vaccine during Phase I Clinical Trials

Group (years)	Reactions	Mild	Moderate	Severe
		% (n/N)*		
Toddler (2-6)	Local	0.00% (0/20)	0.00% (0/20)	0.00% (0/20)
	Systemic	0.00% (0/20)	5.00% (1/20)	0.00% (0/20)
Children (7-15)	Local	0.00% (0/20)	0.00% (0/20)	0.00% (0/20)
	Systemic	5.00% (1/20)	5.00% (1/20)	0.00% (0/20)
Adults (16 and older)	Local	5.00% (1/20)	0.00% (0/20)	0.00% (0/20)
	Systemic	0.00% (0/20)	0.00% (0/20)	0.00% (0/20)
Total	Local	1.67% (1/60)	0.00% (0/60)	0.00% (0/60)
	Systemic	1.67% (1/60)	3.33% (2/60)	0.00% (0/60)

* N = number of subjects included in the safety analysis for each age group. n = number of cases reported for adverse reaction. % = n/N×100%.

Incidence Rates and Severity of Unsolicited Adverse Reactions

No data are currently available for unsolicited adverse reactions of phase I clinical trial.

4.8.1.2 Phase III Clinical Trial

A phase III clinical trial of the vaccine (MPV AC) was conducted in China, including 900 and 10,000 subjects, respectively. The safety profile presented is based on analysis of 600 subjects (above 2 years of age), of which administrated with single dose (0.5 mL) of MPV AC. All subjects were observed for 30 minutes after immunization at the investigation site, and the investigator actively collected the systemic and local reactions at 6, 24, 48 and 72 hours after vaccination, and the adverse events/reactions were reported by the subjects or collected by regular follow-up from Day 4 to Day 30 post-immunization.

Incidence Rates and Severity of Solicited Adverse Reactions

A total of 40 subjects experienced systemic adverse reactions, of which the main body temperature increased, and other symptoms of systemic reactions mainly included: loss of appetite, fatigue, vomiting, headache, drowsiness, irritability, abdominal pain, diarrhea, and rash.

A total of 43 subjects experienced local adverse reactions, of which the main pain at injection site, and other symptoms of local reactions mainly included: itching, swelling, and redness.

The main local reaction and systemic reaction in different age group are mild reactions, the ratio of moderate and severe reaction is low.

The adverse reactions after inoculating the vaccine in domestic clinical trials with 600 subjects (including toddlers, children and adults) are as follows.

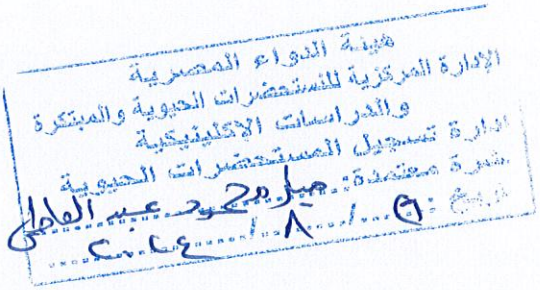

Table 4-2 Adverse Reactions after Vaccination of Group A and C Meningococcal Polysaccharide Vaccine during Phase III Clinical Trials

Group (years)	Reactions	Mild	Moderate	Severe
		% (n/N)*		
Toddler (2-6)	Local	1.50% (3/200)	0.00% (0/200)	0.00% (0/200)
	Systemic	4.50% (9/200)	3.50% (7/200)	1.00% (2/200)
Children (7-15)	Local	10.50% (21/200)	0.50% (1/200)	0.00% (0/200)
	Systemic	5.50% (11/200)	2.00% (4/200)	0.00% (0/200)
Adults (16 and older)	Local	9.00% (18/200)	0.00% (0/200)	0.00% (0/200)
	Systemic	2.00% (4/200)	1.50% (3/200)	0.00% (0/200)
Total	Local	7.00% (42/600)	0.17% (1/600)	0.00% (0/600)
	Systemic	4.00% (24/600)	2.33% (14/600)	0.33% (2/600)

* N = number of subjects included in the safety analysis for each age group. n = number of cases reported for adverse reaction. % = n/N×100%.

Incidence Rates and Severity of Unsolicited Adverse Reactions

No data are currently available for unsolicited adverse reactions of phase III clinical trial.

4.8.1.3 Phase IV Clinical Trial

A phase IV clinical trial of the vaccine (MPV AC) were conducted in China. The safety profile presented is based on analysis of 10,000 subjects (above 2 years of age), of which administrated with single dose (0.5 mL) of MPV AC. All subjects were observed for 30 minutes after immunization at the investigation site, and the adverse events/reactions were collected 7 days after immunization and reported by subjects 30 days after vaccination.

Incidence Rates and Severity of Solicited Adverse Reactions

A total of 1,959 subjects experienced systemic adverse reactions, of which the main fever, and other symptoms of systemic reactions mainly included: fatigue, nausea/vomiting, headache, drowsiness, diarrhea, and rash.

A total of 291 subjects experienced local adverse reactions, of which the main pain, redness and itching at injection site, and other symptoms of local reactions mainly included: induration, swelling, and hypersensitivity.

The main local reaction and systemic reaction in different age group are grade 1 and grade 2 reactions, the ratio of grade 3 and grade 4 reaction is low.

The adverse reactions after inoculating the vaccine in domestic clinical trials with 10,000 subjects (including toddlers, children and adults) are as follows.

Table 4-3 Adverse Reactions after Vaccination of Group A and C Meningococcal Polysaccharide Vaccine during Phase IV Clinical Trials

Group (years)	Reactions	Grade 1	Grade 2	Grade 3	Grade 4
		% (n/N)*			
Toddler (2-6)	Local	1.53% (46/3,000)	0.67% (20/3,000)	0.07% (2/3,000)	0.00% (0/3,000)
	Systemic	15.50% (465/3,000)	7.70% (231/3,000)	0.93% (28/3,000)	0.03% (1/3,000)
Children (7-17)	Local	3.70% (111/3,000)	1.27% (38/3,000)	0.23% (7/3,000)	0.00% (0/3,000)
	Systemic	18.30% (549/3,000)	5.40% (162/3,000)	0.40% (12/3,000)	0.03% (1/3,000)

Adults (18 and older)	Local	1.15% (46/4,000)	0.48% (19/4,000)	0.05% (2/4,000)	0.00% (0/4,000)
	Systemic	10.03% (401/4,000)	2.58% (103/4,000)	0.13% (5/4,000)	0.03% (1/4,000)
Total	Local	2.03% (203/10,000)	0.77% (77/10,000)	0.11% (11/10,000)	0.00% (0/10,000)
	Systemic	14.15% (1415/10,000)	4.96% (496/10,000)	0.45% (45/10,000)	0.03% (3/10,000)

N = number of subjects included in the safety analysis for each age group. n = number of cases reported for adverse reaction. % = n/N×100%.

Incidence Rates and Severity of Unsolicited Adverse Reactions

For phase IV clinical trial, the incidence of unsolicited adverse reactions for MPV AC was 0.037% with most episodes being grade 1 and 2 in severity. The documented symptoms include: upper respiratory infection, cold, fever, pharyngitis, tonsillitis, enteritis, gastroenteritis, bronchitis, urticarial, dizziness.

4.8.2 Post-marketing Experiences

According to the post-marketing data, a total of 111,864,485 doses of MPV AC were distributed from Match 23, 2012 to Match 22, 2023 with 21,167 AEFI reports during the reporting period, a reporting rate of 18.92/100,000 doses can be estimated. The frequency and nature of post-market AEFIs reports are consistent with data generated in clinical trials with the majority of the events of mild to moderate severity.

To report any side effect(s):

Egyptian Pharmacovigilance Centre (EPVC):

Address: 21 AbdelAziz Al Saoud St., Manial ElRawda, Giza, Egypt. E-mail for reporting: pv.followup@edaegypt.gov.eg

Website for reporting: www.edaegypt.gov.eg

Hotline: 15301

Scan QR code:

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إدارة تسجيل المستحضرات الحيوية
أشرة مختصة: ميار محمد عبد الفتاح
تاريخ: ٢٠٢٤/٠٨/٠٩

4.9 Overdose

Overdose with MPV AC is unlikely due to its presentation as a single-dose vial of lyophilized vaccine with corresponding single-dose diluent. No overdose data are available for the product in recipients.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties;

Pharmacotherapeutic group: vaccines; ATC code: J07AH03

5.1.1 Burden of Disease

MPV AC is indicated for the prevention of meningococcal diseases caused by *Neisseria meningitidis* (*N. meningitidis*) serogroups A, C.

Neisseria meningitidis is a fastidious, encapsulated, aerobic gram-negative diplococcus for which human beings are the only host. The bacteria usually reside asymptomatically in the human nasopharynx, and are easily transmitted by direct person-to-person contact or through respiratory droplets from patients or asymptomatic meningococcal carriers. About 1 in 10 people have these bacteria in the back of their nose and throat without being ill. Around 10% to 35% healthy adults have been reported to carry potentially pathogenic *Neisseria meningitidis* in their nasopharynx, especially in populations living in a relatively isolated environment (such as college students and military recruits), who are at high risk of carrying *Neisseria meningitidis*[1]. In most countries, *Neisseria meningitidis* is recognized as a leading cause of meningitis and fulminant septicaemia. *Neisseria meningitidis* causes significant morbidity and mortality in children and young adults worldwide through epidemic or sporadic meningitis and/or septicemia. Clusters and outbreaks are well recognized in all parts of the world. In temperate zones, most cases occur in the winter months. Localized outbreaks occur in enclosed crowded spaces such as dormitories and military barracks. In the "meningitis belt" of sub-Saharan Africa, a region from Ethiopia to Senegal, which includes 18 countries with more than 270 million people, large outbreaks and epidemics occur during the dry season (November to June)[2].

With at least 1.2 million cases reported worldwide each year, invasive meningococcal diseases (IMDs) caused by *Neisseria meningitidis* place a significant global public health concern. Globally, 135,000 deaths are estimated to be attributed to IMD annually[3]. The average case fatality ratio (CFR) of IMD ranges from approximately 10% to 20%, with around 20% of the survivors suffering from long-term disabling sequelae, including cognitive deficit, bilateral hearing loss, motor deficit, seizures, visual impairment, hydrocephalus, and loss of limbs due to tissue necrosis, which are most commonly seen in low-income settings, where the burden of bacterial meningitis is the greatest[4]. The worldwide epidemiology of IMD varies significantly by region. Incidence of meningococcal meningitis is the highest in the African "meningitis belt", with an incidence rate of 10-100 cases per 100,000 population caused by hyperendemic disease and periodic epidemic. The explosive epidemics occur in a cycle of 8-12 years, leading to an incidence rate greater than 1000 cases per 100,000 population. Historically, *N. meningitidis* serogroup A (*Nm*A) caused the majority of meningitis in the belt[5]. Incidence rates of meningococcal diseases range from 2-4 cases per 100,000 population in other parts of the world. By age group, infants younger than 1 year and adolescents/young adults are at increased risk of getting meningococcal infections, which may be attributed to increased social behaviors, while the mortality caused by IMD is the greatest in the

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[1] Background paper on meningococcal vaccines, WHO Strategic Advisory Group of Experts on Immunization, 2011. Geneva, World Health Organization, 2011 (http:// www.who.int/immunization/sage/1_mening_background_document_v5_3___ apr_2011.pdf, accessed November 2011).

[2] WHO|Meningococcal disease. (2021). Retrieved 6 April 2021, from https://www.who.int/ith/diseases/meningococcal/en/

[3] Jafri, R. Z., Ali, A., Messonnier, N. E., Tevi-Benissan, C., Durrheim, D., Eskola, J., Fermon, F., Klugman, K. P., Ramsay, M., Sow, S., Zhujun, S., Bhutta, Z. A., & Abramson, J. (2013). Global epidemiology of invasive meningococcal disease. Population health metrics, 11(1), 17. https://doi.org/10.1186/1478-7954-11-17

[4] Pace, D., & Pollard, A. J. (2012). Meningococcal disease: clinical presentation and sequelae. Vaccine, 30 Suppl 2, B3–B9. https://doi.org/10.1016/j.vaccine.2011.12.062

5 Heather E Reese, Olivier Ronveaux, Jason M Mwenda, Andre Bita, Adam L Cohen, Ryan T Novak, LeAnne M Fox, Heidi M Soeters, Invasive Meningococcal Disease in Africa's Meningitis Belt: More Than Just Meningitis?, *The Journal of Infectious Diseases*, Volume 220, Issue Supplement_4, 1 December 2019, Pages S263–S265, https://doi.org/10.1093/infdis/jiz251

elderly, reaching as high as 20% in the United States[6]. The economic burden of IMD depends on local economic status and the medical insurance mechanism. The average direct costs per IMD case during outbreaks in high-income and low-income countries were estimated at $41,857 to $55,755 and $2,222 (USD) during 1990 to 2010, respectively[7].

The burden of meningococcal diseases also differs in regard of serogroups. A total 13 serogroups have so far been identified for *N. meningitidis*, while the majority of meningococcal infections worldwide are caused by only six serogroups (A, B, C, Y, W135 and X). Serogroup A has been responsible for the largest and most devastating meningococcal outbreaks in sub-Saharan Africa, leading to approximately 300,000 cases and 30,000 deaths in the meningitis belt during 1996-1997[8], while the prevalence in the meningitis belt of Africa has greatly decreased in recent years due to the introduction of MenAfrivac, a vaccine developed for use in sub-Saharan Africa for children and adults between 9 months and 29 years of age against meningococcal bacterium *Neisseria meningitidis* group A. Serogroup B is currently the most important cause of endemic disease in developed countries. In New Zealand, the incidence of meningococcal diseases increased from 1.6 cases per 100,000 population in 1990 to a peak of 17.4 cases per 100,000 population in 2001, with 85% of cases attributed to serogroup B[9]. Serogroup C is responsible for part of the reported endemic disease and localized epidemic outbreaks in developed countries, accounting for 30% of disease in the US and Europe[10].

5.1.2 MPV AC Immunogenicity Clinical Study

5.1.2.1 Immunogenicity in Phase III Clinical Trial

The immune efficacy of group A and C meningococcal polysaccharide vaccine was evaluated by using the meningococcal antibody serum bactericidal test (SBA) recommended by WHO. Serum antibody titers before and after immunization were determined by SBA. The selection of target bacteria and the same group of meningococcal isolated from different strains of vaccine were used. The target bacteria were originated from the China Medical Culture Collection Center.

Efficacy evaluation standard: Meningococcal antibody serum bactericidal test was used to detect serum titer before and after immunization. Pre-immunization, subject with antibody titer < 1:4 was considered as susceptible, and subject with antibody titer ≥ 1:4 was considered as non-susceptible. For the susceptible, the antibody titer ≥1:8 tested by antibody bactericidal assay after immunization was defined as seroconversion. The antibody bactericidal assay of the non-susceptible was defined as positive when the titer was more than 1:16, or reached 4-fold increase post-immunization than titer pre-immunization.

5.1.2.1.1 Antibody Positive Rate and Antibody Level in Susceptible and Non-susceptible Subjects

In the susceptible group, no statistical difference was observed between the antibody seroconversion rate of group A and C meningococcal antibody in all age subjects in study groups and the control group, and the seroconversion rate of antibody after immunization in the study group reached 90%. In addition to adults group, the group C meningococcal antibody geometric

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[6] Vyse, A., Anonychuk, A., Jäkel, A., Wieffer, H., & Nadel, S. (2013). The burden and impact of severe and long-term sequelae of meningococcal disease. Expert review of anti-infective therapy, 11(6), 597–604. https://doi.org/10.1586/eri.13.42

[7] Anonychuk, A., Woo, G., Vyse, A., Demarteau, N., & Tricco, A. C. (2013). The cost and public health burden of invasive meningococcal disease outbreaks: a systematic review. PharmacoEconomics, 31(7), 563–576. https://doi.org/10.1007/s40273-013-0057-2

[8] Hart, C. A., & Cuevas, L. E. (1997). Meningococcal disease in Africa. Annals of tropical medicine and parasitology, 91(7), 777–785. https://doi.org/10.1080/00034989760536

[9] Rouphael, N. G., & Stephens, D. S. (2012). Neisseria meningitidis: biology, microbiology, and epidemiology. Methods in molecular biology (Clifton, N.J.), 799, 1–20. https://doi.org/10.1007/978-1-61779-346-2_1

[10] Jackson, L. A., Schuchat, A., Reeves, M. W., & Wenger, J. D. (1995). Serogroup C meningococcal outbreaks in the United States. An emerging threat. JAMA, 273(5), 383–389.

mean titer (GMT) in study group is higher than that in the control group with significant difference, and no statistical difference was observed regarding each age group's comparison of serum antibody GMT.

In the non-susceptible group, no significant difference was observed in the positive (4-fold increase) rate of group A and C between the study group and the control group. The serum antibody 4-fold increase rate of the all age subjects in study group were greater than 90%. No significant difference was observed between group A and C of all age groups regarding antibody GMT after immunization whether in study group and the control group.

The antibody seroconversion rate, positive rate and GMT of group A and Meningococcal antibody after immunization can be seen in Table 5-1.

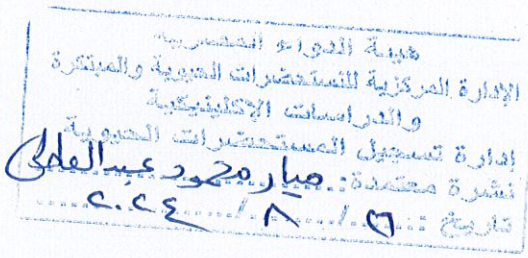


Table 5-1 Antibody Seroconversion, Positive Rate and GMT of Study Group and Control Group after Immunization

Group		Study Group								Control Group								Statistical Analysis							
		Susceptible				Non-susceptible				Susceptible				Non-susceptible				Seroconversion / Positive Rate				GMT			
																		Susceptible		Non-susceptible		Susceptible		Non-susceptible	
		n_1**	N*	Seroconversion Rate & (%)	GMT (95% CI)	n_2**	N*	Positive Rate # (%)	GMT (95% CI)	N*	n_1**	Seroconversion Rate & (%)	GMT (95% CI)	N*	n_2**	Positive Rate # (%)	GMT (95% CI)	x^2	*P*	x^2	*P*	*t*	*P*	*t*	*P*
Infants	A	100	101	99.01	206.50 (175.15-243.46)	66	67	98.51	338.49 (284.58-402.62)	55	56	98.21	198.96 (153.80-257.42)	30	30	100.00	300.94 (222.20-407.58)	0.1005	0.7512	0.1720	0.6783	0.4433	>0.05	1.5515	0.1241
		/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/								
	C	118	120	98.33	375.03 (307.87-456.83)	43	48	89.58	400.55 (273.23-587.32)	51	52	98.08	369.50 (271.66-502.56)	32	34	94.12	481.62 (351.10-660.67)	0.2664	0.6058	0.3810	0.5371	0.1834	0.8547	0.4667	0.6420
Children	A	73	77	94.81	175.10 (146.86-208.77)	112	112	100.00	493.34 (405.08-600.82)	32	33	96.97	145.76 (94.92-223.84)	58	58	100.00	524.39 (432.84-635.29)	0.0000	1.0000	1.5553	>0.05	0.1650	>0.05	0.7308	0.4659
	C	91	93	97.85	307.35 (227.82-414.59)	89	96	92.71	905.72 (703.34-1166.32)	46	48	95.83	346.04 (238.51-502.04)	38	43	88.37	944.71 (679.32-1313.77)	0.0219	0.8823	0.2649	0.4001	0.2499	0.8030	0.8375	0.4038
Adults	A	99	101	98.02	247.19 (197.84-308.86)	87	88	98.86	614.97 (510.28-741.29)	42	42	100.00	273.47 (193.89-377.90)	46	46	100.00	681.72 (552.96-840.46)	0.0187	0.8913	0.1098	0.7404	0.0935	0.9256	0.1326	0.8947
	C	97	97	100.00	1076.52 (876.79-1321.76)	90	92	97.83	1293.40 (1108.02-1509.80)	50	50	100.00	613.11 (415.22-905.31)	36	38	94.74	1184.88 (807.08-1739.54)	No statistical difference		0.1364	0.7119	2.6465	0.0090	0.4420	0.6592
Total	A	272	279	97.49	185.34 (155.75-232.68)	262	267	98.13	477.34 (424.94-536.20)	129	131	98.47	190.35 (164.85-238.28)	134	134	100.00	506.73 (441.40-581.73)	0.0737	0.7860	1.2478	0.2640	0.2147	0.8301	0.3254	0.7450
	C	306	310	98.71	493.77 (425.70-569.89)	221	236	93.64	881.55 (757.18-1026.12)	147	150	98.00	430.03 (345.84-524.72)	106	115	92.17	834.26 (676.53-1028.76)	0.0312	0.8598	0.2624	0.6085	1.4574	0.1457	0.7418	0.4587

* N = number of subjects with a determinate antibody concentration to the given serotype.
** n_1 = number of subjects with an antibody titer ≥1:8 for the given serotype. n_2 = number of subjects with a 4-fold increase of antibody titer for the given serotype.
\# Seroconversion Rate = $n_1/N \times 100\%$.
\# Positive Rate = $n_2/N \times 100\%$.

5.2 Pharmacokinetic Properties;

Not applicable.

5.3 Preclinical Safety Data

Non-clinical data reveal no special hazard for humans based on the studies conducted below.

Table 5-2 Program for Animal Study

Study Type	Study Undertaker	Duration (Days)	Animal Species	Methodology
Allergenic Test	Walvax	21	Guinea pigs	According to "Medical Biological Products Manual" (Jilin Science Press, 1994 edition) recommended method
Acute Toxicity	Walvax	7	Mice	In accordance with the " Compendium of Preclinical Guidelines for New Drugs" recommended method
Abnormal Toxicity	Walvax	7	Guinea pigs and Mice	In accordance with the " Compendium of Preclinical Guidelines for New Drugs" recommended method
Percutaneous Stimulation Test	National Chengdu Center for Safety Evaluation of Drugs	180	Japanese White Rabbits	In accordance with the "Principles of Drug Irritation, Allergic and Hemolytic Study of Technical Guidelines" (May 2014) recommended method
Active Systemic Anaphylaxis	National Chengdu Center for Safety Evaluation of Drugs	150	Guinea pigs	In accordance with the "Principles of Drug Irritation, Allergic and Hhemolytic Study of Technical Guidelines" (May 2014) recommended method
Passive Cutaneous Anaphylaxis	National Chengdu Center for Safety Evaluation of Drugs	150	Guinea pigs	In accordance with the "Principles of Drug Irritation, Allergic and Hemolytic Study of Technical Guidelines" (May 2014) recommended method

Animal allergenic study

Chose 15 healthy guinea pigs weight 250 g-350 g and set trial group, positive and negative control groups. Inoculated the trial group with MPV AC vaccine (produced in pilot plant) at 1st, 2nd, 3rd days, 2 doses/day/guinea pigs, 5 guinea pigs/batch, booster 0.5 mL same batch vaccine 14 days later. Inoculated the positive control group with Bovine serum and negative control with normal saline using the same approach as trial group. Observed any abnormal reaction of the guinea pigs within 30 minutes after inoculation, as well as the health situation of guinea pigs in the following 7 days.

The result showed guinea pigs in the trial group showed no abnormal reaction and had normal weight increase. It demonstrates that MPV AC vaccine does not contain any allergens and proves the product has good safety.

Acute toxicity study

Randomly chose 17-22 g healthy mice to 3 groups containing negative control group. Each group had 20 mice. Injected each mouse with 2 mL of the samples, control with normal saline. Injection concentration was each group containing 250 ug/mL (equal to 10 doses) and 500 ug/mL (equivalent with 20 doses), respectively.

The results showed that the vaccine is safe on mice when injection dosage is 10-person doses/mouse and 20-person doses/mouse. No abnormality was observed. All mice survived and had normal weight increase. It demonstrates the product has good and reliable safety.

Abnormal toxicity study

Abnormal toxicity study was conducted on mice and guinea pigs. In the mice abnormal toxicity study, chose 5 ICR male mice, weight 18-22 g, and intraperitoneal injection one dosage of vaccine with single dose 0.5 mL per animal. In the guinea pig abnormal toxicity study, chose 2 guinea pigs, weight 250-350 g, and intraperitoneal injection ten dosages of vaccine with 10 doses/ 5 mL per animal. Observed the animal appearance and signs, general behavioral activities, mental state, respiratory, genital and perianal, fecal urine, the situation of animal near death or deaths for seven days. The test results showed that each mouse and guinea pig had normal appearance sign, mental, motor state, the natural pores clean, and no obvious abnormal response symptoms. All animals remained healthy and survived, with increase of body weight in the observation period. The abnormal toxicity study complies with the requirement. It demonstrated that the vaccine production process will not introduce toxicity and adding excipients will not increase toxicity.

Percutaneous stimulation test

This study contained 12 groups, including 6 batches of MPV AC vaccine, each batch contained low dosage and high dosage group. Groups for batch 1 and batch 4 had self-control which contained 8 rabbits, other group each contained 4 rabbits. The number of female and male rabbits in each group was equal. Each batch used clinical plan administration dosage. High dosage group was 3 doses (1.5 mL) / side and low dosage group was 1 dose (0.5 mL) / side. In the groups of batch No. 1 and 4, injected subcutaneously outside of right hind limb with the corresponding dosage of vaccine, and outside of left hind limb with the same volume of normal saline 0.9% sodium chloride solution. Injected both sides of the rabbit in other groups with corresponding dosage of the vaccine. Observed the general reaction and injection site reaction after inoculation. 48 hours and 16 days after inoculation, conducted euthanasia for half number of the rabbits in the group, which was taking four rabbits in batch 1 and batch 4 of low dosage and high dosage groups, taking two rabbits in other groups respectively, to conduct histopathological examination on skin, subcutaneous tissue at injection site and corresponding area.

The result showed that within 6 batches of 1 dose/side and 3 doses/side injection of MPV Ac on the Japanese White Rabbit, batch 3 and 4 have slight irritation for 1 dose/side and 3 doses/side dosage. Batch 1 and 2 had slight irritation for 3 doses/side dosage. Other batches were observed with no irritation to the injection site. Observed at the 16th day after injection, the aforementioned irritation completely recovered.

Active systematic Anaphylaxis

This study contained 14 groups, including positive control, negative control, low dosage and high dosage groups of 6 batches of MPV AC vaccine. Each group consist of 3 females and 3 males British Guinea Pigs. Each batch used clinical plan administration dosage. Inoculated 1dose (0.5 mL) / guinea pig of the vaccine sample for the low dosage group and 2 doses (1.0 mL) / guinea pig of the vaccine sample for the high dosage group through subcutaneous injection. Inoculated 1.0 mL / guinea pig of 0.9% sodium chloride solution for the negative group via subcutaneous injection and 0.5 mL/guinea pig of 8 mg / mL oval albumin solution for the positive control group via subcutaneous injection, with one day interval and 3 times of injection. On the 14th and 21st day after the final injection (the 19th and 26th of this study), intravenously inoculated each guinea pig in each group with twice times of the corresponding dosage for stimulation, observed guinea pigs for any possible systematic reaction and death within 30 minutes after inoculation.

The result showed that inoculating one dose 0.5 mL/guinea pig and two doses 1.0 mL / guinea

pigs of 6 batches of the MPV AC vaccine sample through subcutaneous injection is negative.

Passive Cutaneous Anaphylaxis

This study included two phases: 1) antiserum preparation phase: randomly and averagely separated 28 British Guinea Pigs (half female and male) into 14 groups, including positive control, negative control, low dosage groups and high dosage groups of 6 batches of MPV AC vaccine. Each group has two guinea pig, female and male each. Inoculated 1 dose (0.5 mL) / guinea pig of the vaccine sample for the low dosage group and 2 doses (1.0 mL) / guinea pig of the vaccine sample for the high dosage group through subcutaneous injection. Inoculated 1 mL /guinea pig of 0.9% sodium chloride injection for the negative group via subcutaneous injection and 0.5 mL / guinea pig of 8 mg / mL oval albumin solution of the positive control group via subcutaneous injection. Implemented one day interval and 5 times of injection. Took blood samples from aortaventralis of each guinea pig at 10 days after final injection for antiserum preparation. 2) Skin passive sensitization phase: randomly separated 84 British Guinea Pigs (half female and half male) to 14 groups as antiserum preparation phase, half female and male guinea pig. Diluted antiserum prepared in each group to 1:2, 1:8, 1:32 and then injected each guinea pig with 0.1 mL in the corresponding group via single shot in the same injection site on the back skin of guinea pig. 24 hours after sensitization, intravenously injected same dosage of antigen as the dosage used in antiserum preparation, combining with same volume of 1% Evans blue solution. 30 minutes later, conducted euthanasia for each group, measured the diameter of the blue spot of injection site and took photo record.

The result showed that no blue spot appeared in all guinea pig in the negative control group and MPV AC vaccine groups. The positive control groups with each dilution had blue spot at injection site of skin. The diameter of blue spot was larger than 5 mm. The study result demonstrates in the study condition, inoculated with 1 dose (0.5 mL) / guinea pig and 2 / doses (1.0 mL) / guinea pig was negative.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

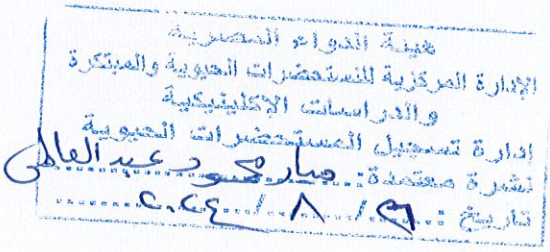
Powder:

Sodium chloride

Lactose

Diluent:

Sterile water for injection



6.2 Incompatibility

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

6.3 Shelf Life

The shelf life of the vaccine is 24 months

6.4 Special Precautions for Storage

Store and ship at 2°C - 8°C, protect from light.

Do not freeze.

6.5 Nature and Contents of Container

Powder in a vial (borosilicate glass) with stopper (chlorobutyl rubber).

Diluent in a vial (borosilicate glass) with stopper (chlorobutyl rubber).

6.6 Special Precautions for Disposal and other Handling

The vaccine must be reconstituted by adding the entire contents of the diluent vial to the vial containing the powder.

The mixture should be well shaken until the powder is completely dissolved in the diluent. After reconstitution, the vaccine is a clear and colourless solution.

The vaccine should be inspected visually for the container, the label, and any foreign particulate matter and/or variation of physical aspect pre-reconstitution, post-reconstitution, and pre-administration. In the abnormal event of either being observed, discard the vaccine.

After reconstitution, the vaccine should be used promptly.

A new disposable syringe should be used to administer the vaccine.

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

7 MARKETING AUTHORIZATION HOLDER

Name: Yuxi Walvax Biotechnology Co., Ltd.

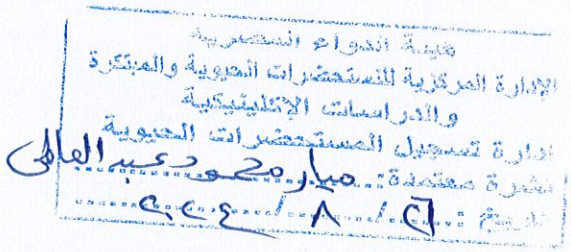
Address: No. 83, South Dongfeng Road, High & New Technology Industries Development Zone, Yuxi, Yunnan Province, China

Zip Code: 653100

Tel: (+86) 877-2076210

Fax: (+86) 877-2076918

Website: www.walvax.com



8 IMPORTED BY

Egyptian Company For Production of Vaccines, Sera and Drugs Egyvac, One of Affiliated Companies of VACSERA

51 Wezaret EL Zeraa ST., Agouza, Giza, Egypt

Tel: (+202)37611111 – Fax: (+202)37483187 Website: www.vacsera.com

9 DATE OF REVISION OF THE TEXT

18th September, 2023