Recombinant B-subunit/ Inactivated Whole Cell Cholera Vaccine

OraVacs™

1 mg /5 x 10^{10} Enteric-Coated Capsule
Oral Vaccine

FORMULATION

Each enteric-coated capsule contains:
Inactivated Whole Cell of *Vibrio cholerae* .....5 x 10^{10}
Recombinant Cholera B subunit .....1 mg

PRODUCT DESCRIPTION

Inactivated Whole Cell of *Vibrio cholerae* Recombinant Cholera B subunit Oral Vaccine (OraVacs™) is an enteric-coated capsule containing a light yellow or a light brown lyophilized powder. It contains inactivated whole *V. cholerae* 01 cells combined with a recombinant B subunit of cholera toxin (rBS-WC).

CLINICAL PHARMACOLOGY

The immunogenicity and safety of lyophilized recombinant, B-subunit and inactivated whole cell vaccine of *Vibrio cholerae* (rBS-WC) were evaluated in randomized, double-blind, placebo-controlled Phase I-III clinical trials involving 11-53 year-old volunteers.

In the Phase 1 trial (n=24; 18-53 years old), the vaccine (OraVacs™) exhibited two to four-fold higher rise in titer of vibriocidal antibody and four-fold higher rise in titer of antitoxin than the placebo group. Only one patient reported nausea as an adverse effect.

In the Phase II trial (n=300); 11-49 years old), the vaccine (OraVacs™) had the same positive returning rate, increased vibriocidal antibody and cholera toxin antibody as the reference vaccine. Only one patient experienced abdominal pain.

In the Phase III trial, 6,079 adult volunteers (17-38 years old) were randomly divided into three groups: one was treated with high dose vaccine (1 mg rBS and 1x10^{11} WC), another with low dose (1 mg rBS and 5x10^{10} WC), and the third group with placebo as control. The immunogenicity and safety of lyophilized rBS-WC were evaluated in terms of average antibody level, antibody conversion rates and incidence of adverse reaction. Comparison between low-dose and high-dose groups did not reveal any significant difference for antibody levels in serum or stool ($p>0.05$); antibody levels in the placebo group did not have any significant change during the study. Conversion rates for vibriocidal antibody (Vab), anticholera toxin (anti-CT), and anti- lipopolysaccharide (anti-LPS) were all above 83% in both serum and stool. The difference in antibody conversion rate between the low-dose and high-dose groups was not statistically significant ($p>0.05$). The respective levels of Vab, anti-LPS and anti-CT antibodies in the vaccine groups were 2.8-6.8, 2.3-5.1, 4.6-14.8 times higher than those in the placebo group. These levels were still 2.8, 2.3 and 4.6 times higher than pre-vaccine levels 12 months after the first vaccine dose. The levels for Vab, anti-LPS and ani-CT antibodies in stool were 2-6.8, 6.2-9.3 and 2.6-6.7 times higher than those in the placebo group, respectively. Anti-CT peaked around 56 days after vaccination. Protective efficacy assessment against diarrhea caused by Enterotoxigenic *E. coli* was also done. Results showed that the incidence of diarrhea caused by heat labile toxin-producing *Escherichia coli* (LT-ETEC) in the vaccine group was significantly lower than that in the control group ($p<0.001$). The protection against LT-ETEC diarrhea conferred by rBS-WC can last at least half a year. Average protection rate of rBS-WC against LT-ETEC in the vaccine groups was 69.88% at 3 months and 54.99% at 6 months.

A study of 100 adults (18-20 years old) on oral cholera vaccine (OraVacs™) demonstrated that an alternate dosing schedule is as effective as the standard vaccination procedure (see **DOSAGE AND ADMINISTRATION**)

INDICATIONS

For active immunization against cholera and/or travelers' diarrhea caused by Enterotoxigenic *Escherichia coli* (ETEC) in adults and children ≥ 11 years old in high-risk work and residential environment.

DOSAGE AND ADMINISTRATION

The use of oral cholera vaccine (OraVacs™) should be determined on the basis of official recommendations taking into consideration the variable epidemiology and risk of contracting the disease in different geographical areas and traveling conditions.

Oral cholera vaccine (OraVacs™) should be used as an additional public health tool and should not replace standard protective measures such as potable drinking water, adequate sanitation /hygiene and health education.

In the event of diarrhea, rehydration measures should be instituted.

Primary Immunization for Adults and Children ≥ 11 years old:
For those who are to be immunized for the first time, take one capsule each day on day 0, 7 and 28.

It is recommended to take the first dose at least 2 weeks before visiting an endemic country.

Alternate Dosing Schedule for Adults:
Take two capsules on day 0, then one capsule on day 7 for exceptional cases, eg., emergency prevention in military, cholera outbreak in emergent conditions or travel will take place within a month or less of starting the vaccine course.

Booster Dose:
For those who have had previous immunization, take three capsules the same way as the primary immunization before the prevalent season.

CONTRAINDICATIONS

- Known hypersensitivity to any component of the vaccine, or patients who have shown signs of hypersensitivity after previous administration of cholera vaccine.
- Patients with severe hypertension, heart, liver and kidney diseases, HIV and active tuberculosis.

WARNINGS / PRECAUTIONS

Before administering the vaccine, a competent physician is required for proper guidance.

- Prior to immunization, the patient's medical history should be reviewed for possible sensitivity to the vaccine.
- For better result, take the vaccine 2 hours after meals and do not take any food within 1 hour after vaccination.
- Avoid eating raw, cold, oily, sour, or spicy foods for two days after taking the vaccine.
- Postpone intake if there is acute illness, including infection or febrile diseases unless recommended by a physician.
- As with any vaccine, a protective immune response may not be elicited in all vaccines.

Due to the brittleness of the enteric-coated capsule, carefully peel off the foil from the edge of flat side when taking out the capsule to avoid breakage.

INTERACTION WITH OTHER MEDICAMENTS

- **Antibiotics:** Since antibiotics may interfere with the effectiveness of the vaccine, individuals on antibiotic therapy should wait 7 days after completion of therapy before taking oral cholera vaccine.
- **Vaccines and Other Medicinal Products:** Oral administration of other vaccines and medicinal products should be avoided 1 hour before and 1 hour after vaccination.

Preliminary results from a clinical study involving a limited number of volunteers showed no interaction with the antibody response to an inactivated oral cholera vaccine when a live oral vaccine (enterocapsules) against typhoid was given simultaneously with an inactivated oral cholera vaccine. The immune response to live typhoid vaccine was not investigated in this study.

Likewise when a yellow fever was given concomitantly with an inactivated oral cholera vaccine, no interaction was observed with this immune response to the yellow fever vaccine. The immune response to the inactivated oral cholera vaccine was not studied.

No other vaccines/medicinal products including oral polio vaccine and antimalarials, have been given simultaneously with an inactivated oral cholera vaccine in clinical trials.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy and Lactation: No clinical studies have been conducted among pregnant or lactating women. Use of the vaccine in this population is not recommended.

UNDESIRABLE EFFECTS

Adverse effects (AEs) experienced by volunteers during the clinical trials were low. In a Phase III clinical trial in 6,079 adults 17-38 years old, the incidence of AEs was 0.84% in volunteers who took the oral cholera vaccine (OraVacs™). Among those reported were abdominal pain or discomfort after taking the vaccine, urticaria, nausea, and diarrhea. These symptoms were mild, resolved spontaneously after 1-3 days.

The safety of oral cholera vaccine (OraVacs™) was assessed in a separate clinical trial in 412 volunteers. Results showed that 27 (6.55%) volunteers experienced side effects. Three volunteers with dizziness and headache and one volunteer who had constipation withdrew from the study. The main side effects among the rest of the volunteers were abdominal pain and diarrhea/loose stool. One volunteer had transient palpitation. All patients recovered without treatment. The older age group (70 years old and above) had the highest number of side effects (37.04%). No statistical difference in the occurrence of side effects between males and females was observed.

Fever, malaise, respiratory symptoms, gastrointestinal disturbances, anaphylaxis and hypersensitivity reactions may also occur.

The following adverse drug reactions have been reported with other oral cholera vaccine: vomiting, abdominal cramps, stomach/abdominal gurgling (gas), flatulence, dyspepsia, gastroenteritis, loss of/or poor appetite, dehydration, drowsiness, insomia, fainting, reduced sense of taste, respiratory symptoms (including rhinitis, cough, dyspnea, increased sputum), sore throat, sweating, rash, joint pain, pain, flu-syndrome, asthenia, paresthesia, chills/shivers, fatigue, lymphadenitis, angioedema, pruritus, hypertension.

OVERDOSAGE & MANAGEMENT

There have been no reports of overdosage.

STORAGE CONDITIONS

- Store at temperatures between 2°C-8°C. Do not freeze.
- Keep the product out of sight and reach of children.

AVAILABILITY: Aluminum Foil, Pack of 3's

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADVERSE DRUG REACTION

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at **www.fda.gov.ph** AND Unilab at **(+632) 858-1000** or **productsafety@unilab.com.ph**. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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