For the use of Registered Medical Practitioner or Hospital or Laboratory only

Cholera Vaccine (Inactivated, Oral) I.P.

Shanchol®

PRESCRIBING INFORMATION

Qualitative and Quantitative Composition

Each oral dose of 1.5 mL contains

Active ingredients	**Quantity**
V. cholerae O1 Inaba E1 Tor strain Phil 6973 formaldehyde killed	600 Elisa Units (EU) of lipopolysaccharide (LPS)
V.cholerae O1 Ogawa classical strain Cairo 50 heat killed	300 EU of LPS
V.cholerae O1 Ogawa classical strain Cairo 50 formaldehyde killed	300 EU of LPS
V.cholerae O1 Inaba classical strain Cairo 48 heat killed	300 EU of LPS
V.cholerae O139 strain 4260B formaldehyde killed	600 EU of LPS
Excipients	
Thiomersal I.P.	Not more than 0.02% (w/v)
Buffer	q.s to 1.5 mL

THERAPEUTIC INDICATIONS

Shanchol is indicated for active immunization against *Vibrio cholerae.* The vaccine can be administered to anyone above the age of 1 year. Data for the safety and efficacy of the vaccine in infants (less than 1 year of age) is not available. The earliest onset of protection can be expected 7-10 days after the completion of the primary series of the vaccine.

POSOLOGY

The recommended dose of the vaccine (1.5 mL) is to be administered orally. The primary immunization schedule consists of two doses given at an interval of at least two weeks. Shanchol **should not be administered parenterally (intramuscularly, subcutaneously or intravenously). The vaccine is only recommended for oral administration.**

CONTRA-INDICATIONS

Shanchol should not be administered to subjects with either known hypersensitivity to any component of the vaccine, or having shown signs of hypersensitivity after previous administration of the vaccine. Formaldehyde is used during the manufacturing process and trace amounts may be present in the final product. Caution should be taken in subjects with known hypersensitivity to formaldehyde. As with all products, the possibility of allergic reactions in persons sensitive to components of the vaccine should be evaluated. As with other vaccines, immunization with the **Shanchol** should be delayed in the presence of any acute illness, including acute gastrointestinal illness or acute febrile illness. A minor illness such as mild upper respiratory tract infection is not a reason to postpone immunization.

WARNINGS AND SPECIAL PRECAUTIONS

Vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and the possible occurrence of undesirable events) and a clinical examination. As with any vaccine, immunization with the Shanchol may not protect 100% of susceptible persons. **This vaccine is not a substitute for therapy in case of individuals suspected to be suffering from cholera or showing signs and symptoms of an acute episode of gastrointestinal disease or acute watery diarrhea.**

Immuno-compromised persons (subsequent to a disease or immunosuppressive therapy) may not obtain the expected immune response after vaccination with the Shanchol. If possible, in the opinion of the medical practitioner, due consideration should be given to postponing vaccination until after the completion of any immunosuppressive treatment.

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As with all vaccines, appropriate medical treatment should always be readily available in case of a rare event of anaphylactic reactions following the administration of the vaccine. For this reason, it is recommended that the vaccinee should remain under medical supervision for at least 30 minutes after vaccination.

SPECIAL POPULATIONS

HIV / AIDS

The safety and immune response of **Shanchol** has not been clinically evaluated in individuals with HIV/AIDS. However, Shanchol is a killed vaccine administered orally and acts locally in the intestine. Therefore, theoretically, the vaccine is not expected to increase the risk of cholera in an individual with HIV/AIDS but the vaccine may not elicit the expected immune response and protection due to underlying immune-suppressive state.

Pregnancy and Lactation

No specific clinical studies have been performed to evaluate the safety and immunogenicity of **Shanchol** in pregnant or lactating women and for the fetus. **The vaccine is therefore not recommended for use in pregnancy or during lactation**. However, **Shanchol** is a killed vaccine that does not replicate, is given orally and acts locally in the intestine. Therefore, in the theory, Shanchol should not pose any risk to the human fetus. Administration of **Shanchol** to pregnant or lactating women may be considered after careful evaluation of the benefits and risks in case of a medical emergency or an epidemic.

Pediatric population

Data for the safety and efficacy of the vaccine in infants (less than 1 year of age) is not available. **The vaccine is thus not recommended for use in infants.**

KNOWN ADVERSE REACTIONS ASSOCIATED WITH Shanchol

The following adverse events are known to occur with **Shanchol** use. Acute Gastroenteritis, Diarrhea, Fever, Vomiting, Abdominal pain, Itching, Rash, Nausea, Weakness, Cough, Vertigo, Dryness of mouth, Oral ulcer (rare), Sore throat (rare) and Yellowing of urine (rare). It has been observed that the incidence of adverse events is less after the second dose as compared to the first.

MECHANISM OF ACTION

Shanchol consists of killed *V.cholerae*. It has been shown to be effective to administer the vaccine orally, which induces local immunity. The vaccine acts locally in the gastrointestinal tract to induce an IgA antibody response (including memory) comparable to that induced by cholera disease itself. The antibacterial intestinal antibodies prevent the bacteria from attaching to the intestinal wall thereby impeding colonization of *V.cholerae* O1 and *V.cholerae* O139. The protection against cholera is specific for both biotype and serotype.

CLINICAL EXPERIENCE

A double-blind, randomized, placebo controlled trial was conducted in Kolkata, India. A total of 101 (50 vaccine and 51 placebo) healthy adults (males and non-pregnant females) aged 18-40 years and 100 (50 vaccine and 50 placebo) healthy children and adolescents (males and non-pregnant females) aged 1-17 years were administered two doses of Shanchol or placebo at an interval of two weeks. Following 2 dose immunization, 53% of adult and 80% of children vaccinees showed a ≥ 4 fold rise in serum *V. cholerae* O1 vibriocidal antibody titers. This study showed that a 2-dose regimen of Shanchol is safe, well-tolerated, and immunogenic in a cholera-endemic area.[1]

A cluster randomized double blind placebo controlled field trial was conducted in Kolkata, India. This pivotal Phase III clinical trial was conducted to evaluate the efficacy and safety of the two-dose primary regimen of Shanchol in a cholera-endemic area in Kolkata, in preventing episodes of culture-confirmed *Vibrio cholerae* O1 diarrhea severe enough for the patient to seek treatment in a health-care facility. A total of 66,900 subjects aged one year or older were administered two doses of Shanchol or placebo at an interval of at least two weeks. The trial subjects were followed up for a total period of five years after vaccination. Over five years of follow up there were 69 episodes of cholera in the vaccine group and 219 episodes in the placebo group. Shanchol provided 65% protection against clinical significant *V. cholerae* O1 in an endemic area for at least five years after vaccination. Overall protection was sustained for 5 years follow-up.

Significant differences in the cumulative 5 year vaccine protection among different age groups at vaccination were not detected. Vaccine protection was clearly evident in the third to fifth year of follow-up in persons vaccinated at ages five years and older and during the second year in children vaccinated at 1-4 years of age. There were no statistically significant differences in the occurrence of reported adverse events between recipients of vaccine and placebo. The most common adverse events reported were diarrhea, fever, vomiting and abdominal pain. This study conducted in subjects aged one year or older (no upper age limit) along with the other non-pivotal studies formed the basis for the licensure and WHO pre-qualification of Shanchol.[2,3,4]

Shanchol also confers herd protection as demonstrated in the above study using geographic information system (GIS) analysis. In the GIS analysis, herd protection was assessed by evaluating association between vaccine coverage among the population residing within 250 m of the household and the occurrence of cholera in that population. Using this approach, the risk of cholera among placebo recipients was demonstrated to be inversely related to neighborhood-level vaccine coverage, and the trend was highly significant ($P < 0.01$).[5]

A double blind placebo controlled safety and immunogenicity study was conducted in Dhaka, Bangladesh. A total of 330 subjects - 110 adults and 220 children (more than 1 year of age), were administered 2 doses of Shanchol or placebo at an interval of two weeks. Overall, the seroconversion (≥ 4 fold rise in serum vibriocidal antibodies) against *V.cholerae* O1 Inaba, *V.cholerae* O1 Ogawa and *V.cholerae* O139 was observed in 72.53% (60% in adults and 78.8% in children), 74.83% (in 72 % in adults and 76.25% in children) and 46.2% (21% in adults and 58.8% in children) vaccine recipients respectively as compared to 5.5% (7.3% in adults and 4.5% in children), 6.7% (9.2% in adults and 5.5% in children) and 7.2% (5.4% in adults and 8.15% in children) in the placebo groups respectively ($p<0.001$ for each comparison). No significant differences were observed in safety events between the vaccine and placebo recipients.[6]

Immune responses after one and two doses of Shanchol oral cholera vaccine were measured in a double-blind, randomized, placebo-controlled trial of 77 adults aged 18-40 years and 77 children aged 1-17 years residing in Kolkata, India. Overall 65% of adults and 87% of children and 46% of adults and 82% of children exhibited a ≥ 4- fold rise in serum *V.cholerae* O1 vibriocidal antibody titers from baseline following dose 1 and 2, respectively. Responses to *V.cholerae* O139 were less pronounced but followed a similar pattern. This study demonstrated that in a cholera-endemic area, the vaccine elicited vibriocidal responses even after a single-dose of the vaccine.[7]

An open label post licensure trial to evaluate the safety and immunogenicity of Shanchol was conducted in Vellore, a cholera-endemic area in India. A total of 200 subjects - 100 adults and 100 children (more than 1 year of age) were administered 2 doses of Shanchol at an interval of two weeks. Seroconversion (≥ 4 fold rise in serum vibriocidal antibodies) against *V.cholerae* O1 Inaba was observed in 68% adults, 80.2% children after 1st dose and in 55.7% adults, 68.8% children after 2nd dose; against *V.cholerae* O1 Ogawa was observed in 47.4% adults, 72.9% children after 1st dose and in 45.4% adults, 67.7% children after 2nd dose; against *V.cholerae* O139 was observed in 19.6% adults, 26% children after 1st dose and in 20.6% adults, 18.8% children after 2nd dose. No serious adverse event was reported during the trial. The commonly reported solicited AEs in adults and children were general ill feeling and headache.[8]

In 2012, Shanchol was introduced in Haiti as a pilot project to demonstrate the acceptability and feasibility of the use of Shanchol. In Urban Haiti, 52,357 persons received dose 1 of the vaccine and 90.8% received dose 2; estimated coverage of the at-risk community was 75%. In rural Haiti, 45,417 persons were successfully vaccinated with Shanchol in the region, and 90.8% of these persons completed their second dose. The project confirmed the acceptability and feasibility of use of Shanchol. The good safety profile of the Shanchol vaccine was also further confirmed in this pilot study in the Haitian population; only mild side effects were registered in a thorough post-vaccination monitoring effort.[9,10]

In Guinea in 2012, the first mass vaccination campaign using a two-dose oral cholera vaccine (Shanchol) as an additional control measure to respond to the ongoing nationwide cholera epidemic, was organized. This was the first large-scale use of oral cholera vaccine as an outbreak control measure in Africa; 312,650 doses of vaccine were administered during two vaccination rounds in two coastal districts in Guinea. The feasibility, timeliness of implementation, and delivery cost were similar to those of other mass vaccination campaigns. The campaign was well accepted by the population,

and high vaccination coverage was achieved. No severe adverse events were notified.[11,12]

Pharmaceutical Form

Shanchol is suspension for oral administration.

SHELF - LIFE

The expiry date of the vaccine is indicated on the label and packaging.

SPECIAL PRECAUTIONS FOR STORAGE

Shanchol should be stored at +2ºC to +8ºC. **Do not freeze**. Discard if vaccine has been frozen.

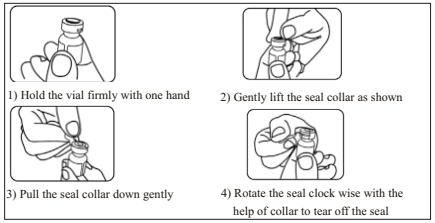
PRESENTATION

Glass vials containing 1.5 mL as a single dose.

INSTRUCTION FOR USE/ HANDLING

The vaccine is presented as a suspension. After vigorous shaking of the vial, 1.5 mL should be poured into the mouth of the recipient. The vaccine administration may be optionally followed by water to facilitate ingestion, if needed. The vaccine can alternatively be administered, in younger individuals, using a disposable syringe (without needle) to withdraw the contents from the vial, which are then squirted into the mouth of the recipient. **Shanchol should not be administered parenterally (intramuscularly/subcutaneously or intravenously). The vaccine is only recommended for oral administration.**

Instruction to Open Tear- down Aluminium Seal:



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