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

# Cholera Vaccine (Inactivated, Oral) B.P.

# Shanchol™

## PRESCRIBING INFORMATION

### Qualitative and Quantitative Composition

**Each oral dose of 1.5 mL contains**

| **Active Ingredients** | **Quantity** |
|---|---|
| *V. cholerae* O1 Inaba El 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 B.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 two to four weeks.[1] **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 also 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.

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.

**DRUG INREACTIONS**

Shanchol is not yet recommended for use in age group less than one year and hence the data to support co-administration of **Shanchol** with other childhood vaccines administered less than one year of age has not been generated. Interaction with other vaccines used in older age groups have not been evaluated.

However, inactivated vaccines are not known to interfere with the immune response to other inactivated vaccines or to live vaccines. An inactivated vaccine can be administered either simultaneously or at any time before or after a different inactivated vaccine or live vaccine.[4]

However in the absence of specific data, there is a theoretical risk that the components of oral inactivated Cholera vaccine (**Shanchol**) might interfere with oral live vaccines such as oral live Polioviruses vaccines.

**SPECIAL POPULATIONS**

**HIV/AIDS**

The safety and immune response of **Shanchol** has been clinically evaluated in 25 adults with HIV infection in Haiti.[2] Subjects with serious chronic illness were excluded. The median CD4+ T-cell count (cells/μL) of the subjects with HIV infection was 433 and the interquartile range was 344–574. Seroconversion after vaccination a ≥ 4 fold increase from the baseline vibriocidal titer occurred at a rate of 65% against the Ogawa serotype and 74% against the Inaba serotype in subjects with HIV infection. The study results suggest that the vaccine may provide immunity with moderate HIV infection. There were no reported adverse events related to vaccination.[2]

**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.Hence, theoretically 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 the context of mass vaccination campaigns to prevent or control outbreaks.

During a mass-vaccination campaign conducted in Guinea, 1312 pregnant women had received at least one dose of **Shanchol.** There was no statistically significant evidence of a negative pregnancy outcome (pregnancy loss, miscarriage, and stillbirth) or fetal malformation following **Shanchol** exposure during pregnancy.[3]

Please consult national recommendations for guidance on the use of oral cholera vaccine during pregnancy.

**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 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.. **Shanchol** provided 65% protection against clinical significant *V. cholerae* O1. 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**. [5-7]

The immunogenicity of **Shanchol** was evaluated in a subset of 137 trial participants (adults and children aged one year and above) at 14 days after the second dose and at one year after the first dose. There were 5.7 and 5.8 geometric mean fold (GMF) rises in titers to *V. cholera* Inaba and Ogawa, respectively at 14 days after the second dose and 1.7 and 2.8 GMF rises respectively after one year. No significant differences in the GMF-rises were observed among the age groups. The results demonstrated that although vibriocidal antibody response declined after one year, the vaccine remained protective five years after vaccination.[8]

**Shanchol** also confers herd protection as demonstrated in the above pivotal Phase III clinical trial 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 ($P < 0.01$).[9]

The safety and immunogenicity of the two-dose regimen of **Shanchol** were also confirmed in additional studies (Table 1).[1, 10-15] The results demonstrated that in a cholera-endemic area, the vaccine elicited vibriocidal responses even after a single-dose of the vaccine. In a study conducted to compare the immunogenicity of two dosage regimens, two doses given at 14 day interval versus two doses given at 28 day interval, comparable immune responses between the two dosing schedules were observed.[1] The study results support the option for flexible dosing regimen for **Shanchol**. The 2nd dose of the primary vaccination can be therefore given between 2 and 4 weeks after the 1st dose. Another study conducted to evaluate booster dose regimen of Shanchol, demonstrated that a two-dose booster or single-dose booster given five years after the primary series elicits an immune response similar to those receiving a primary series in endemic areas.[15]So a booster dose regimen is recommended after five years from primary vaccination in adults and children aged five years and above. In children aged below five years, a booster dose regimen will be needed after two years from primary vaccination. A two-dose booster in cholera non-endemic areas and a single booster dose in cholera endemic areas are recommended.

Table 1: Safety and immunogenicity studies using two-dose regimen of **Shanchol.**

| Study | No.of subjects enrolled | %Subjects with seroconversion (≥ 4 fold rise in antibody titers) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | O1 Inaba | | O1 Ogawa | | O139 | |
| | | | Adults | Children | Adults | Children | Adults | Children |
| #India (Kolkata)[10] | 201 | After 2 doses¶ | 53 | 80 | - | - | 10 | 27 |
| #Bangladesh[11] | 330 | 1st dose | 60 | 65 | 70 | 62 | 19 | 55.1 |
| | | 2nd dose¶ | 57 | 74 | 59 | 75 | 19 | 39.5 |
| #India (Kolkata)[12] | 160 | 1st dose | 65 | 87 | - | - | 8.3 | 38.5 |
| | | 2nd dose¶ | 46 | 82 | - | - | 6 | 28 |
| $India (Vellore)[13] | 200 | 1st dose | 67.7 | 80.2 | 47.9 | 72.9 | 19.6 | 26 |
| | | 2nd dose¶ | 55.2 | 68.8 | 45.8 | 67.7 | 20.6 | 18.8 |
| #Ethiopia[14] | 216 | 1st dose | 70 | 74 | 65 | 80 | 28 | 53 |
| | | 2nd dose¶ | 81 | 77 | 70 | 84 | 30 | 43 |
| $Philippines [13] | 336 | 1st dose | 83* | 87.9 | 77.7* | 85.7 | 42* | 66.1 |
| | | 2nd dose¶ | 78.4* | 87.9* | 68.5* | 90.2 | 35.1* | 55.8 |
| #India (Kolkata)[1] | 356 | 2 doses; 14 day interval | 55 | 80 | 45 | 73 | 20 | 28 |
| | | 2 doses; 28 day interval | 58 | 77 | 49 | 72 | 20 | 20 |
| #India (Kolkata)[15] | 426 | Primary 2-dose series | 60* | 79 | 53* | 72 | - | - |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 1-dose booster§ | 57* | 85 | 55* | 70 | - | - |
| | | 2-dose booster§ | 51* | 82 | 41* | 66 | - | - |

#Randomized, double blind placebo controlled study; $ Open label, single arm study; ¶ 2nd dose at 14 days post 1st dose; *in subjects aged ≥15 years; § Booster dose given five years post primary vaccination.

These lower immune responses to O139 may have been due to limitations in the sensitivity of the assay used. Moreover, although vibriocidal titers to O1 are considered as indicators of immune stimulation, the relationship of vibriocidal titers to O139 with protection against O139 cholera still remains unclear.[1,7]

The first dose of the vaccine may have elicited memory immune response among previously exposed individuals residing in Kolkata, India (a cholera-endemic area) resulting in a brisk rise in vibriocidal titers after the first dose with no further rises after the second dose. It is also hypothesized that the first dose of vaccine stimulated an immune response in the intestinal mucosa and that this response may have blocked uptake of the second dose of the vaccine. Therefore decreasing vibriocidal titers after the second dose may be the result of the natural waning of antibodies.[7]

Effectiveness of the two-dose regimen of Shanchol has been confirmed in case-control studies during mass vaccination campaigns in India, Haiti, and Guinea and in a cluster-randomised open-label trial in Bangladesh (Table 2).[21-24]

Table 2: Mass vaccination campaigns using two-dose regimen of Shanchol and vaccine effectiveness

| Vaccination Campaign | No. of Subjects receiving 1st dose (% coverage) | Drop-out rate between the 2 doses | Vaccine Effectiveness (95% CI; P value) | Duration of effectiveness evaluation period |
|---|---|---|---|---|
| Urban Haiti[16] | 52,357 (75%) | 9.2% | - | - |
| Rural Haiti [17,22] | 45,417 (76.7%) | 9.2% | *63% (8–85; P=0.031) | 2 years |

| | | | | |
|---|---|---|---|---|
| Coastal Guinea [18,19,23] | 172,544 (>90%) | ~14% | *86.6% (56.7–95.8; P=0.001) | 6 months |
| Rural Odisha, India [20,24] | 31,552 (61%) | 25% | *69% (14.5 - 88.8) | 2 years |
| Dhaka, Bangladesh [21] | 141,839 (82%) | 13% | ¶ 37% against severely dehydrating cholera (13-55; p=0.002) in vaccination group; and 45% (19-63; p=0.001) in vaccination and behavioural change group | 2 years |

*Vaccine effectiveness evaluated in case-control study. Cases were patients seeking treatment for laboratory-confirmed *V. cholerae* - associated diarrhea.

¶ Cluster-randomised open-label trial conducted in a highly mobile urban population setting. 267,270 residents in 90 clusters were randomly assigned (1:1:1) to vaccination only, vaccination and behavioural change (safe drinking water and hand washing), or no intervention. Overall protective effectiveness was assessed as the risk of severely dehydrating cholera during 2 years after vaccination for all individuals present at time of the second dose, irrespective of their vaccination status.[21]

**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.

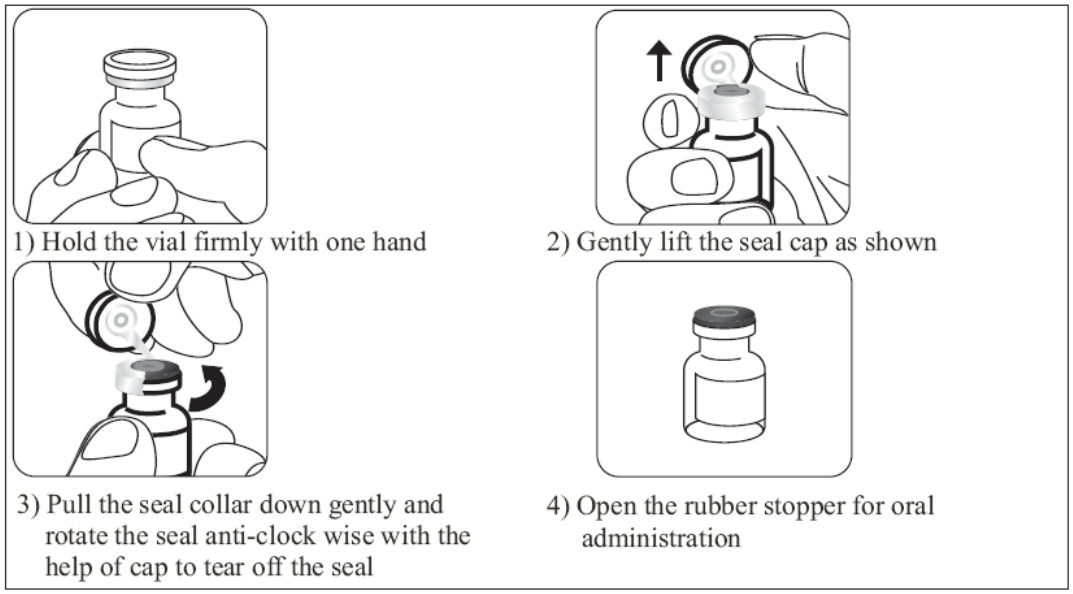
## PRESENTATION

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 Flip off Tear-down Seal:**

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