SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF MEDICINAL PRODUCT : Shanchol

2 GENERIC NAME : Cholera Vaccine (Inactivated, Oral) B.P.

3 QUALITATIVE AND QUANTITATIVE COMPOSITION:

Cholera vaccine is an inactivated suspension of killed whole cells of the four different *V. Cholerae* bacterial strains. Monovalent cultures of each strain are killed by heat or formaldehyde treatment. Names of the four strains are given below;

Strain A- *Vibrio cholerae* O1, Inaba, Cairo 48 (heat killed)
Strain B- *Vibrio cholerae* O1, Ogawa, Cairo 50 (heat killed and formaldehyde killed)
Strain C- *Vibrio cholerae* O139, 4260B (formaldehyde killed)
Strain D- *Vibrio cholerae* O1, Inaba, El Tor Phil 6973 (formaldehyde killed)

Each killed monovalent culture is then concentrated and diafiltered to produce Monovalent bulks (Drug Substance). These bulks are formulated to produce the final bulk vaccine.

Each oral dose of 1.5mL contains:

S. No.	Name of the Component(s)	Quantity per Single-dose
1	*V.cholerae* O1, Inaba El Tor strain Phil 6973 formaldehyde killed	600 ELISA Units (EU) of lipopolysaccharide (LPS)
2	*V.cholerae* O1, Ogawa classical strain Cairo 50 heat killed	300 EU of LPS
3	*V.cholerae* O1 Ogawa classical strain Cairo 50 formaldehyde killed	300 EU of LPS
4	*V.cholerae* O1, Inaba classical strain Cairo 48 heat killed	300 EU of LPS
5	*V.cholerae* O139, strain 4260B formaldehyde killed	600 EU of LPS
6	Thiomersal B.P.	Not more than 0.02% (w/v)
7	Buffer	Q.S. to 1.5 mL

4 PHARMACEUTICAL FORM:

Suspension for Oral Administration.

5 CLINICAL PARTICULARS:

5.1 Therapeutic Indication:

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 vaccination.

5.2 Posology and Method of administration:

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 to four weeks. **Shanchol** should not be administered parenterally (intramuscularly, subcutaneously or intravenously). The vaccine is only recommended for oral administration.

5.3 Contraindications:

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 **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.

5.4 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.

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 vaccine should remain under medical supervision for at least 30 minutes after vaccination.

5.5 Interaction with other medicinal products and other forms of interaction:

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. Interactions with other vaccines used in older age groups have not yet 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.

5.6 Special Populations:

HIV/AIDS:
The safety and immune response of **Shanchol** has been clinically evaluated in 25 adults with HIV infection in Haiti. 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 $\geq$ 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 suggests that the vaccine may provide immunity with moderate HIV infection. There were no reported adverse events related to vaccination.

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 and 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**.

5.7 Undesirable effects:

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.

5.8 Effect on ability to drive and use machines:

There are no anticipated adverse effects on ability to drive and use machines.

5.9 Overdose:

There is no data on overdose of **Shanchol** vaccine.

6 PHARMACOLOGICAL PROPERTIES:

6.1 Pharmacodynamic properties:

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.

6.2 Pharmacokinetic properties:

Not applicable.

6.3 Pre-clinical Safety data:

Formal preclinical toxicology studies have not been performed because there are no relevant animal models for studying the effects of an oral cholera vaccine.

6.4 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 cholera-endemic area in Kolkata, in preventing episodes of culture-confirmed *Vibrio cholerae* O1 diarrhea severe enough for 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 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. cholerae* 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 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
	200	1st dose	67.7	80.2	47.9	72.9	19.6	26

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 (Vellore)[13]		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.

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. cholera*-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.

7 PHARMACEUTICAL PARTICULARS:

7.1 List of Excipients:

S.No.	Name of the Excipients	Quantity per Single-dose
1.	Thiomersal B.P.	Not more than 0.02% (w/v)
2.	Buffer	q.s. to 1.5 mL

q.s - Quantity sufficient.

7.2 Incompatibilities:

The vaccine should not be mixed with any other vaccine or Pharmaceutical product.

7.3 Shelf-Life:

30 months from the date of manufacture.

7.4 Special precautions for storage:

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

7.5 Nature and content of container:

Shanchol is supplied in glass vials containing 1.5 mL as a single dose.

7.6 Instruction for use and handling:

The vaccine is presented as a suspension. After vigorous shaking of the vial, 1.5 mL should be squirted 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, especially in younger individuals, with 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.

8 MARKETING AUTHORIZATION HOLDER:

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