Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT (GENERIC NAME)

Cholera Vaccine (Inactivated, Oral) I.P.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 1.5 mL contains:
V. cholerae (O1 El Tor Hikojima serotype recombinant strain)
Formaldehyde inactivated whole cell ..... ≥ 900 µg of LPS
Phosphate buffered saline..... q.s. to 1.5 mL

3. PHARMACEUTICAL FORM (DOSAGE FORM AND STRENGTH) Suspension for Oral Administration in single dose (1.5 mL) respule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

For active immunization against Diarrhoeal infection caused by *V. cholerae* to the children, adolescents and adults aged 1 year and above with administration of two doses on Day 0 and Day 14.

4.2 Posology and method of administration

Two doses of 1.5mL of **HILLCHOL ®** are to be administered orally with an interval of two weeks (doses on Day 0 and Day 14)

[INSTRUCTION FOR USE]

- The vaccine should be administered to children, adolescents and adults aged 1 year and above.
- Two doses of vaccine should be given at an interval of two weeks.
- The vaccine is presented as a suspension. Therefore, after shaking the vaccine container rigorously, 1.5 mL of the vaccine should be squirted into the mouth.
- Give a sip of potable water (particularly to children) after administering the vaccine that has an unpleasant taste to avoid vomiting (does not have to be given to each person vaccinated)
- The vaccine is only presented in a liquid form. Frozen forms of this vaccines are not permitted and should be discarded
- The vaccine should not be administered parenterally (intramuscularly, subcutaneously or intravenously). The vaccine is only recommended for oral administration.

4.3 Contraindications

- The vaccine should not be administered to persons with either known hypersensitivity to any component of the vaccine, or having shown signs of severe reaction to the previously taken dose.
- Immunization with **HILLCHOL ®** should be delayed in the presence of any acute illness, including acute gastrointestinal illness or acute febrile illness.

4.4 Special warnings and precautions for use

- Like all other vaccines, supervision and appropriate medical treatment should always be available to treat any anaphylactic reactions following immunization. Vaccinees should remain under medical supervision for at least 30 minutes after vaccination.

- Concurrent illness: As with other vaccines, administration of **HILLCHOL®** should be postponed in individuals suffering from an acute severe febrile illness/acute infection.

4.5 Interaction with other medicinal products and other forms of interaction (Drug Interactions)
No interaction studies have been performed.

4.6. Use in special populations (Such as pregnant women, lactating women, pediatric patients, geriatric patients etc.) (Pregnancy and lactation)
No data available

4.7 Effects on ability to drive and use machines
No studies for the effect of **HILLCHOL®** on the ability to drive and use machines have been performed

4.8 Undesirable effects

Phase 1/2: Safety and Immunogenicity trial
A phase 1/2 randomized, open-labeled safety and immunogenicity clinical trial of **HILLCHOL ®** OCV (Oral Cholera Vaccine) was conducted in Mirpur area of Dhaka, Bangladesh from July 2016 to May in 2017 (registered at ClinicalTrials.gov; registration no. NCT02823899).

The WHO prequalified Shanchol™ OCV was used as the comparator. The study evaluated **HILLCHOL®** vaccine with two different potency; not less than 600 µg /ml and not less than 900 µg /ml total O1 LPS as measured by Inhibition ELISA along with comparator vaccine.

A total of 840 healthy participants, with 280 individuals each receiving **HILLCHOL®** (high dose vaccine), **HILLCHOL®** (low dose vaccine) and Shanchol™ (comparator vaccine). The study was conducted in three age descending cohorts consisting of Group I - 360 participants of age 18 - 45 years ("adults"), Group II- 240 participants of age 5 - 17 years ("older children") and Group III 240 participants of age 1 - <5 years ("younger children"). Participants in each cohort were randomized to receive either test or comparator vaccine. As low dose was found to be inferior in terms of immunogenicity to high dose and Shanchol; it was decided to focus on the high dose only for further development.

All 820 participants enrolled in the study (20 subject's loss to follow-up) were included in the safety analysis. The total number of solicited symptoms were similar amongst High dose with 9.2% (95% CI; 6.8-11.6) Low dose with 8.5% (95% CI; 6.2-10.8) and comparator vaccine groups 9.6% (95% CI; 7.1-12.1) as per attached Phase 1/2 Clinical study report.

Safety of 2 doses of **HILLCHOL®** formulations A and B evaluated in human population aged 1 year and above in three age cohorts. Safety analysis was done for 820 participants in total, who completed the study as per protocol compliance. All safety events were compared to comparator vaccine Shanchol™ in age cohort independently.

For solicited AEs, the occurrence rate of AE was compared for each group in both **HILLCHOL®** formulations with the comparator vaccine. No significant difference was observed in the rate of occurrence between **HILLCHOL®** high dose, **HILLCHOL®** low dose, and comparator arms.

In the adult age cohort, the commonest solicited AE observed was weakness, at a frequency of 4.2% in Shanchol™ recipients 3.3%, and 4.2% in **HILLCHOL®** high and low dose recipients. This was followed by vertigo observed in 3.8% of Shanchol™ recipients and 2.9% and 3.3% in **HILLCHOL®** high and low dose recipients.

Among older children, nausea is the commonest AE in Shanchol™ recipients 4.5% and vertigo is the commonest in **HILLCHOL®** high dose recipients 3.8%. Similarly, among younger children diarrhoea and fever are the commonest AE in Shanchol recipients 3.8%, and vomiting and cough are the commonest in **HILLCHOL®** high dose recipients 3.1%.

The frequency of AEs after the first dose was slightly higher across age groups for (Shanchol ™ 12.9% and **HILLCHOL®** both high and low dose each of 10.4% vaccine recipients after the first dose), then second dose, 6.2%, 8.1%, and 6.5% respectively for Shanchol™ and **HILLCHOL®** high and low dose vaccine recipients.

For unsolicited AEs, 13 cases were observed in total with no significant difference in distribution between **HILLCHOL®** high dose, low dose control vaccine. Out of 13 unsolicited AEs, only 2 cases were rated grade 3 severity in nature. All unsolicited AE resolved without any complication or sequelae. There were no SAEs reported during the entire duration of the study, in any of the age cohorts.

Phase 3-Safety and Immunogenicity study

A phase 3 randomized, modified double-blind, multi-centric, comparative study, to evaluate the non-inferiority of immunogenicity and safety of single strain oral cholera vaccine **HILLCHOL®** (BBV131) to the comparator vaccine Shanchol™ along with lot-to-lot consistency of **HILLCHOL®** (BBV131) was conducted in India with CTRI registration No: CTRI/2022/01/039734.

A total of 1800 participants in 3 age groups; Group 1: ≥18 years, Group 2: ≥5 to <18 and Group 3: ≥1 to <5 years. Participants in each age group were randomised to receive either **HILLCHOL®** (3 lots) or Shanchol™ in 1:1:1:1 ratio. In each age group **HILLCHOL®** recipients were 450 and Shanchol™ recipients were 150.

All the 1800 subjects followed up till day 180.

A total of 257 AEs were reported from 236 (13.1%) subjects in the study. The AE incidence was similar across the study age Groups I, II and III, and comparable for the **HILLCHOL®** (BBV131) and Shanchol™ arms.

In the Group I (Age ≥ 18 years), a total of 85 AEs were reported from 77 (12.8%) subjects – 68 AEs in 61 (13.6%) subjects from **HILLCHOL®** (BBV131) arm, and 17 AEs from 16 (10.7%) subjects from Shanchol™ arm.

In the Group II (Age ≥ 5 to < 18 years), a total of 95 AEs were reported from 87 (14.5%) subjects – 74 AEs in 66 (14.7%) subjects from **HILLCHOL®** (BBV131) arm, and 21 AEs from 21 (14.0%) subjects from Shanchol™ arm.

In the Group III (Age ≥ 1 to < 5 years), a total of 77 AEs were reported from 72 (12.0%) subjects – 58 AEs in 53 (11.8%) subjects from **HILLCHOL®** (BBV131) arm, and 19 AEs from 19 (12.7%) subjects from Shanchol™ arm.

Of the 257 reported AEs, 216 AEs in 206 (11.4%) subjects were considered related to the vaccine – 167 AEs in 158 (11.7%) subjects of **HILLCHOL®** (BBV131) group and 49 AEs in 48 (10.7%) subjects of Shanchol™ group.

Overall in the study, the commonly reported AE Participants (occurring in ≥ 1% overall subjects) were oropharyngeal pain [1.9% overall; 2.0% in **HILLCHOL®** (BBV131) and 1.8% in Shanchol™ arms], dry mouth [1.8% overall; 1.9% in **HILLCHOL®** (BBV131) and 1.6% in Shanchol™ arms], pyrexia [1.8% overall; 1.7% in **HILLCHOL®** (BBV131) and 2.0% in Shanchol™ arms], nausea [1.4% overall; 1.5% in **HILLCHOL®** (BBV131) and 1.3% in Shanchol™ arms], headache [1.4% overall; 1.2% in **HILLCHOL®** (BBV131) and 2.2% in Shanchol™ arms], cough [1.3% overall, 1.4% in **HILLCHOL®** (BBV131) and 1.1% in Shanchol™ arms], and vomiting [1.1% overall; 1.4% in **HILLCHOL®** (BBV131) and 0.2% in Shanchol™ arms].

Solicited Adverse Events:
Overall, 202 solicited AEs were reported by 195 (10.8%) subjects during 7-day follow-up period after overall, 2 doses – 116 solicited AEs [in 116 (6.4% subjects)] were reported during the 7-day follow-up period after Dose 1 and 86 solicited AEs [in 86 (4.8%) subjects] were reported during the 7-day follow-up period after Dose 2. Of the overall 202 solicited AEs during the 7- day follow-up period in the study, 74 AEs were reported from 70 subjects (11.4%) in Group I, 67 AEs from 65 (10.8%) subjects in Group II, 61 AEs from 60 (10.0%) subjects in Group III. The incidence of solicited AEs during the 7-day follow-up period were comparable across all study age groups and for **HILLCHOL®** (BBV131) and Shanchol™ arms. A majority of these solicited AEs (197 of 202 AEs) were of mild severity, 5 solicited AEs were of moderate severity; none were severe.

The commonly reported solicited AE Participants (occurring in ≥ 1% overall subjects) during 7-day follow-up period after overall dose were oropharyngeal pain [1.9% overall; 1.9% in **Hillchol®** (BBV131) and 1.8% in Shanchol™ arms], dry mouth [1.8% overall; 1.9% in **HILLCHOL®** (BBV131) and 1.6% in Shanchol™ arms], nausea [1.4% overall; 1.5% in **HILLCHOL®** (BBV131) and 1.3% in Shanchol™ arms], headache [1.2% overall; 1.0% in ® (BBV131) and 2.0% in Shanchol™ arms], cough [1.1% overall, 1.1% in **HILLCHOL®** (BBV131) and 1.1% in Shanchol™ arms], and vomiting [1.1% overall; 1.4% in **HILLCHOL®** (BBV131) and 0.2% in Shanchol™ arms].

The commonly reported solicited AE Participants during 7-day follow-up period after dose 1 were nausea [1.1% overall; 1.1% in **HILLCHOL®** (BBV131) and 1.1% in Shanchol™ arms] and oropharyngeal pain [1.0% overall; 1.0% in **HILLCHOL®** (BBV131) and 0.9% in Shanchol™ arms], dry mouth [0.8% overall; 0.9% in **HILLCHOL®** (BBV131) and 0.7% in Shanchol™ arms], vomiting [0.8% overall; 1.0% in **HILLCHOL®** (BBV131) and 0.2% in Shanchol™ arms], headache [0.8% overall; 0.7% in **HILLCHOL®** (BBV131) and 1.1% in Shanchol™ arms], and cough [0.6% overall; 0.4% in **HILLCHOL®** (BBV131) and 0.9% in Shanchol™ arms].

The commonly reported solicited AE Participants during 7-day follow-up period after dose 2 were dry mouth [1.0% overall; 1.0% in **HILLCHOL®** (BBV131) and 0.9% in Shanchol™ arms], oropharyngeal pain [0.9% overall; 0.9% in **HILLCHOL®** (BBV131) and 0.9% in Shanchol™ arms], and cough [0.6% overall, 0.7% in **HILLCHOL®** (BBV131) and 0.2% in Shanchol™ arms].

All the solicited AEs reported during the 7-day follow-up period post dose were considered related to the study vaccine.

Majority of the solicited AEs reported in the study were mild in nature, and none of the solicited AEs were severe.

All local solicited AEs were mild in nature; none were moderate or severe.

The 5 solicited AEs with moderate intensity were systemic AEs reported by subjects in **HILLCHOL®** (BBV131) arm and included headache (1 subject in Group I), abdominal pain upper (2 subjects in Group II, 1 subject in Group III), and pyrexia (1 subject in Group III).

Unsolicited Adverse Events:
Overall, 54 unsolicited AEs were reported from 46 (2.6%) subjects during the entire study period - 43 unsolicited AEs in 35 (2.6%) subjects from the **HILLCHOL®** (BBV131) group and 11 unsolicited AEs in 11 (2.4%) subjects from the Shanchol™ group. Pyrexia was the most common unsolicited AE (1.1%), followed by diarrhoea (0.5%), nasopharyngitis (0.3%), headache (0.3%), and cough (0.2%), with a comparable incidence across the **HILLCHOL®** (BBV131) vs. Shanchol™ arms for all the study groups. Of the 54 reported unsolicited AEs [46 (2.6%) subjects], 13 AEs in 12 (0.7%) subjects were considered related to the study vaccine: 10 AEs in 9 (0.7%) in **HILLCHOL®** (BBV131) vs. 3 AEs in 3 (0.7%) subjects in Shanchol™]. Related unsolicited AEs in the study included diarrhoea (0.4%); pain, nasopharyngitis, and sneezing (0.1% each) with no major differences between the vaccine arms across the study groups.

Overall, during the 14-day follow-up period after overall dose in the study, 12 unsolicited AEs were reported from 12 (0.7%) subjects: 9 (0.7%) subjects in the **HILLCHOL®** (BBV131) and 3 (0.7%) subjects in the Shanchol™ arms. Of the 12 unsolicited AEs during 14-day follow-up period, 8 AEs occurred in 8 (0.4%) subjects during 14-day follow-up post Dose 1, and 4 AEs occurred in 4 (0.2%) subjects during 14-day follow-up post Dose 2.

Group I (Age ≥ 18 years) reported no unsolicited AEs during the 14-day follow-up period. Group II (Age ≥ 5 to < 18 years) reported 10 unsolicited AEs from 10 (1.7%) subjects during the 14-day follow-up period: 1.6% in **HILLCHOL®** (BBV131) vs. 2.0% in Shanchol™ arms. Group III (Age ≥ 1 to < 5 years) reported 2 unsolicited AEs from 2 (0.3%) subjects during the 14-day follow-up period: 0.4% in **HILLCHOL®** (BBV131) vs. 0.0% in Shanchol™ arms.

All the unsolicited AEs occurring during the 14-day follow-up period were mild; none were severe. The reported unsolicited AEs during the 14-day follow-up period were diarrhoea [8 (0.4%)], and pain [2 (0.1%)], nasopharyngitis [1 (0.1%)], and sneezing [1 (0.1%)], with no major differences between the study vaccine arms across the study age groups.

Outcome of all the 257 AEs reported in the study were considered as recovered/resolved.

Safety Conclusions:
The overall incidence of solicited AEs and unsolicited AEs during the entire study was similar across subjects receiving **HILLCHOL®** (BBV131) or Shanchol™ for all study age Groups I, II, and III.

There were no immediate AEs reported within 30 minutes post each dose in any subject in the study.

There were no reports of any medically attended AEs (MAAEs), AE of special interest (AESI), serious adverse events (SAEs), AEs leading to discontinuation or death from any subject in the study.

To conclude, vaccination with **HILLCHOL®** (BBV131) was well-tolerated with no unexpected safety concerns raised over a period of 6 months post vaccination. **HILLCHOL®** (BBV131) vaccine exhibited a good reactogenicity profile, and all adverse events (solicited, unsolicited, and other AEs) were well balanced between **HILLCHOL®** (BBV131) and Shanchol™ arms for all the study groups.

4.9 Overdose
No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action
HILLCHOL® is a vaccine that contains formalin-inactivated bacteria from a stable recombinant strain of *Vibrio cholerae* O1 El Tor Hikojima serotype. This strain expresses of approximately 50% each of Ogawa and Inaba antigens. When administered orally, the vaccine has been proven to be effective in inducing local immunity in the gastrointestinal tract. The vaccine functions by inducing an antibody response locally, which prevents the bacteria from attaching to the intestinal wall. This, in turn, impedes colonization of both *V. cholerae* O1. It's important to note that the protection against cholera is specific to both the biotype and serotype.

5.2 Pharmacodynamic properties
Pharmacotherapeutic group: Vaccine, ATC code: J07AE01

Cholera is an acute diarrheal infection caused by oral intake . of food or water contaminated with the bacterium *Vibrio cholerae* of serogroup O1 and O139. O1 has two biotypes, classical and El Tor, and three serotypes, Ogawa, Inaba and Hikojima (rare). The Ogawa and Inaba strains are agglutinated by their own respective specific sera, while Hikojima strain is agglutinated by both Ogawa and Inaba anti-sera. **HILLCHOL®**; a novel cholera vaccine consists of formalin-inactivated bacteria of a stable recombinant *Vibrio cholerae* O1 El Tor Hikojima serotype strain expressing approximately 50% each of Ogawa and Inaba O1 LPS antigens.

A phase 3 randomized, modified double-blind, multi-centric, comparative study, to evaluate the non-inferiority of immunogenicity and safety of single strain oral cholera vaccine **HILLCHOL®** (BBV131) to the comparator vaccine Shanchol™ along with lot-to-lot consistency of **HILLCHOL®** (BBV131).

A Phase III multicentric clinical study compared non-inferiority, safety, and an immunological lot-to-lot consistency of **HILLCHOL®** (BBV131) with control vaccine in three different age cohorts (≥18 years, ≥5 to <18 and ≥1 to <5 years), enrolled a total of 1800 participants and all the participants received the two doses of vaccine on day 0 and day 14.

The study measured the vaccine-induced immune response of participants who received the **HILLCHOL®®** vaccine and a control vaccine.

Anti-Ogawa Antibody Titers:
Pre-immunization GMT of anti-Ogawa antibody of **HILLCHOL®®** vaccine cohort is 33.9 [30.68, 37.53] and in individually Group 1, Group 2 and Group 3 participants titers are 41.0 [33.86, 49.72], 33.1 [28.12, 39.06], 28.7 [24.34, 33.88] respectively.

Post-immunization with two doses of **HILLCHOL®®** vaccine GMT; Seroconversion (SCR) of anti-Ogawa antibody titer is 249.1 [227.89, 272.35]; SCR 68.25 [65.69, 70.74] and in individually Group 1, Group 2 and Group 3 participants titers are 270.1 [235.22, 310.22]; SCR 69.11 [64.62, 73.35], 261.7 [221.23, 309.69]; SCR 67.11 [62.54, 71.46], 218.6 [187.11, 255.45]; 68.53 [64.00, 72.80] respectively.

Vaccine induced immune response persistence was assessed till 6 months and anti –Ogawa antibody titer is 71.9 [65.07, 79.36] and in individually Group 1, Group 2 and Group 3 participants titers are 76.7 [65.24, 90.27], 75.8 [64.40, 89.27], 63.8 [52.76, 77.09] respectively.

Pre-immunization GMT of anti-Ogawa antibody of control vaccine cohort is 29.7 [25.02, 35.34] and in individually Group 1, Group 2 and Group 3 participants titers are 34.1 [24.67, 47.13], 31.3 [23.26, 42.09], 24.7 [18.65, 32.63] respectively.

Post-immunization with two doses of control vaccine GMT; Seroconversion (SCR) of anti-Ogawa antibody titer is 261.3 [225.32, 303.14]; SCR 67.93 [63.39, 72.23] and in individually Group 1, Group 2 and Group 3 participants titers are 274.2 [209.68, 358.55]; SCR 69.80 [61.75,

77.04], 284.8 [225.36, 359.94]; SCR 66.67 [58.52, 74.14], 228.7 [174.29, 299.97]; SCR 67.33 [59.21, 74.76] respectively.

Vaccine induced immune response persistence of anti –Ogawa antibody titer in control vaccine cohort is 83.6 [70.42, 99.27] and in individually Group 1, Group 2 and Group 3 participants titers are 70.8 [54.39, 92.11], 95.6 [73.46, 124.30], 86.5 [60.29, 124.18] respectively.

Anti-Inaba Antibody Titers:
Pre-immunization GMT of anti-Inaba antibody of **HILLCHOL®** vaccine cohort is 20.7 [18.78, 22.89] and in individually Group 1, Group 2 and Group 3 participants titers are 20.7 [17.36, 24.66], 21.4 [18.06, 25.29], 20.2 [16.99, 23.93] respectively.

Post-immunization with two doses of **HILLCHOL®** vaccine GMT; Seroconversion (SCR) of anti-Inaba antibody titer is 196.3 [178.58, 215.86]; SCR 69.52 [66.98, 71.97] and in individually Group 1, Group 2 and Group 3 participants titers are 198.4 [168.71, 233.38]; SCR 69.33 [64.84, 73.57], 201.4 [171.00, 237.22]; SCR 70.02 [65.54, 74.24], 189.4 [160.13, 223.9]; 69.20 [64.69, 73.44] respectively.

Vaccine induced immune response persistence was assessed till 6 months and anti –Inaba antibody titer is 64.5 [58.35, 71.38] and in individually Group 1, Group 2 and Group 3 participants titers are 58.2 [49.06, 69.07], 66.1 [55.68, 78.47], 70.0 [58.34, 83.87] respectively.

Pre-immunization GMT of anti-Inaba antibody titer of control vaccine cohort is 25.1 [21.09, 29.96] and in individually Group 1, Group 2 and Group 3 participants titers are 25.1 [18.48, 34.08], 21.6 [16.23, 28.77], 29.3 [21.18, 40.50] respectively.

Post-immunization with two doses of control vaccine GMT; Seroconversion (SCR) of anti-Inaba antibody titer is 194.9 [168.90, 224.96]; SCR 67.48 [62.93, 71.80] and in individually Group 1, Group 2 and Group 3 participants titers are 205.7 [157.96, 267.98]; SCR 69.80 [61.75, 77.04], 189.0 [143.76, 248.49]; SCR 69.33 [61.29, 76.59], 190.5 [154.85, 234.43]; SCR 63.33 [55.08, 71.04] respectively.

Vaccine induced immune response persistence of anti-Inaba antibody titer in control vaccine cohort is 71.0 [58.95,85.41] and in individually Group 1, Group 2 and Group 3 participants titers are 53.7 [39.63, 72.77], 88.2 [65.79,118.13], 75.6 [52.49,109.00] respectively.

Based on historical data we observed a slight decrease in GMT following 2-dose interval, which is a well-established phenomenon.

Lot-Consistency:
A lot-to-lot consistency for **HILLCHOL®** (BBV131) immune response was demonstrated based on comparable anti-Ogawa and anti-Inaba serotype antibody titres seroconversion rate across all 3 Lots.

The lot-to-lot consistency evaluation for **HILLCHOL®** was also essential to provide an assessment of manufacturing consistency in addition to the information provided on the manufacturing process. In the phase 3 study the batch-wise comparison of GMTs of anti-

Ogawa and anti-Inaba antibodies for **HILLCHOL®** (BBV131) group was studied and the criterion for consistency of 3 lots of **HILLCHOL®** (BBV131) was two-sided 95% CI for GMT ratio of any 2 lots had lower limit ≥ 0.667 and upper limit ≤ 1.5.

Description	**Hillchol®** (BBV131)		**Hillchol®** (BBV131)		**Hillchol®** (BBV131)	
	Lot 1 (N=447)	Lot 2 (N=449)	Lot 1 (N=447)	Lot 3 (N=449)	Lot 2 (N=449)	Lot 3 (N=449)
Seroconversion rate: Anti-Ogawa vibriocidal antibody titer (IU/mL)						
n (%)	295 (66.00)	312 (69.49)	295 (66.00)	311 (69.27)	312 (69.49)	311 (69.27)
95% CI #	-0.0349 [-0.096, 0.026]		-0.0327 [-0.094, 0.029]		0.0022 [-0.058, 0.063]	
Seroconversion rate: Anti-Inaba vibriocidal antibody titer (IU/mL)						
n (%)	319 (71.36)	296 (65.92)	319 (71.36)	320 (71.27)	296 (65.92)	320 (71.27)
95% CI #	0.0544 [-0.006, 0.115]		-0.0010 [-0.058, 0.060]		-0.0535 [-0.114, 0.007]	
# The 95% CIs were calculated by a likelihood score method						

The Phase 3 study data has proven that **HILLCHOL®** vaccine is non-inferior [The non-inferiority criterion – lower bound 95% CI ≥ -10%] in terms of safety and immunogenicity to the WHO pre-qualified control vaccine in all the age groups. The vaccine's immune response was consistent across three lots and were non-inferior to each other, meeting regulatory requirements.

The Phase 3 study data has proven that **HILLCHOL®** (BBV131) to be non-inferior to the WHO pre-qualified control vaccine in all the age groups for immunogenicity based on seroconversion rates against Ogawa and Inaba serotypes, following 2 doses across all age groups. Lot-to-lot consistency for **HILLCHOL®** (BBV131) immune response was demonstrated, and were non-inferior to each other, meeting regulatory requirements. The **HILLCHOL®** vaccine was well-tolerated with no unexpected safety concerns raised over 6 months post-vaccination.

5.3 Pharmacokinetic properties
Evaluation of pharmacokinetic properties is not required for vaccines.

6. PRECLINICAL SAFETY DATA (NON-CLINICAL PROPERTIES)

6.1 Animal Toxicology or Pharmacology
Pre-clinical studies were performed both by Bharat Biotech International Limited and MSD Welcome Trust Hilleman Laboratories Private Limited, from whom this Technology has been licensed. These studies were performed as per the regulatory guidelines, in both rodent (Sprague Dawley &Wistar Rats) and non-rodent (New Zealand White Rabbits) models, upon administration of N+1 dose regimen (3doses) at 14-day interval by Oral route, followed by 14-day recovery period. Safety was well tolerated and there were no treatment related changes observed, in any of the tested parameters such as clinical pathology, gross pathology and microscopic investigations. Moreover, all animals showed good immunogenicity, by eliciting antigen specific IgG and IgA binding titers. Further, abnormal toxicity studies conducted in mice and guinea pigs, as per the regulatory guidelines, also revealed that the vaccine is safe, with no mortality and no abnormal clinical signs, in any of the animals tested.

7. DESCRIPTION

Cholera Vaccine (Inactivated, Oral) (**HILLCHOL®**) is a Uniform, turbid brownish suspension free of aggregates and extraneous particles.

8. PHARMACEUTICAL PARTICULARS

8.1 List of excipients

HILLCHOL® contains Phosphate Buffered Saline

8.2 Incompatibilities

The vaccine should not be mixed with any other medicinal products or active immunizing agents.

8.3 Shelf-life

The expiry date of **HILLCHOL®** is indicated on the label and carton of the vaccine.

9. NATURE AND CONTENTS OF CONTAINER (PACKAGING INFORMATION)

1.5mL (single dose) oral suspension in a respule (polyethylene) presented in a multi-monodose (5 single dose) respules connected by a strip bar.

9.1 Storage and Handling Instructions

9.1.1 Special Precautions for Storage

The Vaccine should be stored at **+ 2°C to + 8°C**.

Do not freeze. Discard if the vaccine has been frozen. Vaccine will be seriously damaged if the frozen at temperatures below 0°C.

Keep out of reach of children.

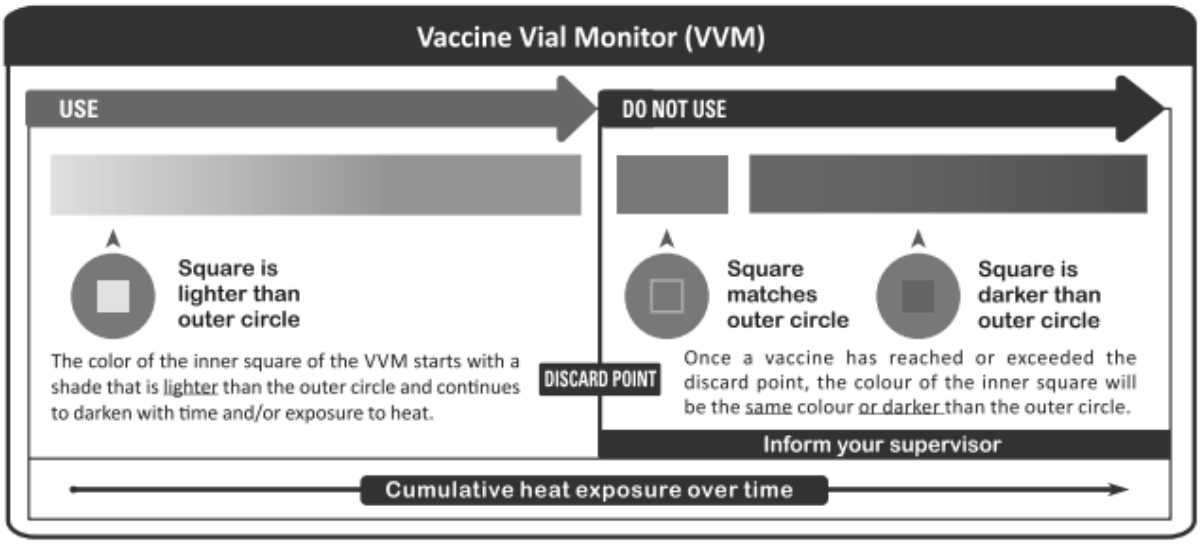
Shake well before use.

Do not use the vaccine after the expiration date shown on the label.

Discard the used oral respules in approved biological waste containers according to local regulations.

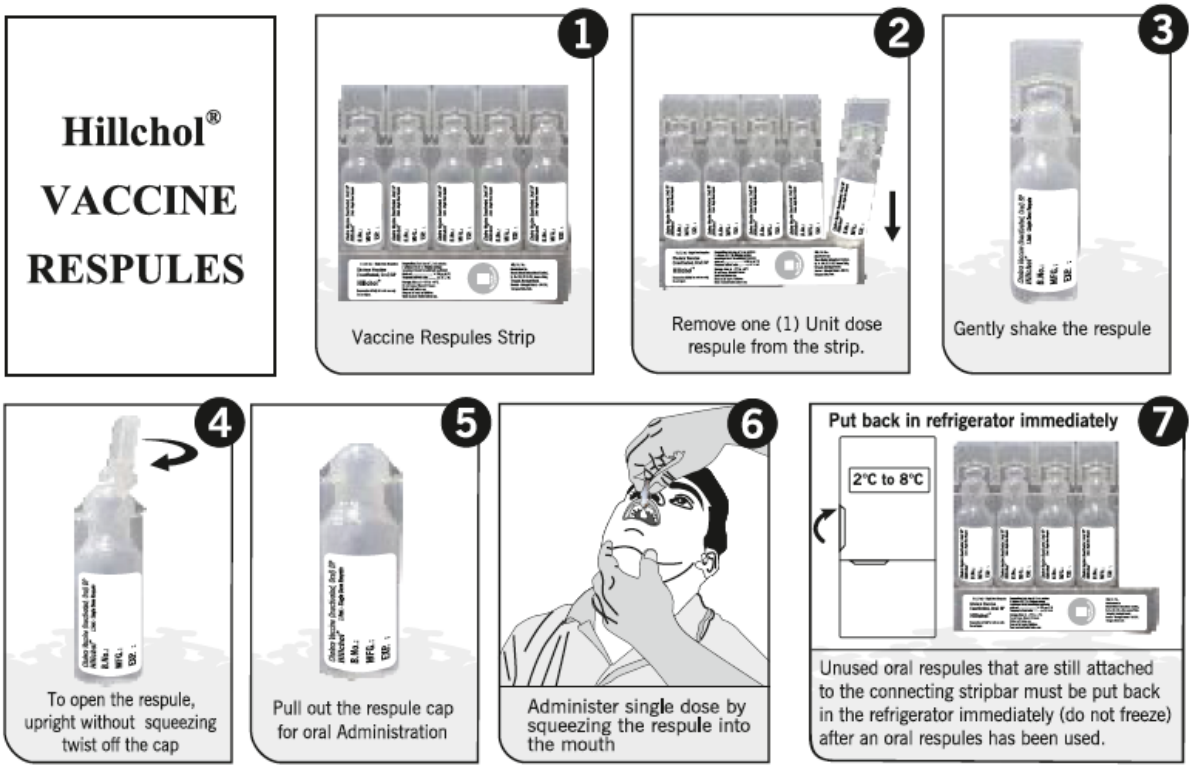
The Vaccine Vial Monitor:

The Vaccine Vial Monitors (VVM) are on the label of **HILLCHOL®** vaccine supplied through Bharat Biotech International Limited. The colour dot that appears on the label on the connecting strip bar of the multi-monodose (5 dose) respules is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the respules have been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.



The interpretation of the VVM is simple. Focus on the inner square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the outer circle, then the vaccine can be used. As soon as the colour of the inner square is the same colour as the outer circle or of a darker colour than the outer circle, then the tubes should be discarded.

Administration of HILLCHOL® vaccine:



9.1.2 Special precautions for disposal

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

10. PATIENT COUNCELLING INFORMATION

HILLCHOL® is a cholera vaccine that helps to prevent cholera. It is an oral vaccine that comes in the form of a uniform, turbid brownish suspension that is free from aggregates and extraneous particles. Each dose of the vaccine is 1.5mL and contains *V.cholerae* (O1 El Tor Hikojima Serotype recombinant strain) formaldehyde Inactivated Whole Cell that is equal to or greater than 900µg of LPS.

The most common side effects of the vaccine include oropharyngeal pain, dry mouth, headache, cough, vomiting, weakness, vertigo, fever, and nausea. Although it is rare, there is a chance of a severe allergic reaction (anaphylaxis) occurring.

As a precaution, the vaccinator may ask you to wait for 30 minutes after each dose of the vaccination at the place where you receive the vaccine. This is to monitor you for adverse reactions if any. If you experience any side effects or adverse reactions, please contact or visit your healthcare provider or vaccinator.

11. MARKETING AUTHORISATION HOLDER (DETAILS OF MANUFACTURER)

Manufactured & Marketed by

Bharat Biotech International Limited,
Sy. No. 230, 231 & 235, Genome Valley,
Turkapally, Shamirpet Mandal,
Medchal-Malkajgiri District – 500 078, Telangana State, India.
Email: feedback@bharatbiotech.com
Toll free number: 1800 102 2245

12. DETAILS OF MARKETING AUTHORISATION NUMBER(S) (DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE)

MF/BIO/24/000043

DATE OF FIRST MARKETING AUTHORISATION

16 April 2024

13. DATE OF REVISION

24 January 2025