Central Drugs Standard Control Organization

Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India
FDA Bhavan, ITO, Kotla Road, New Delhi -110002

Annexure - III

SUMMARY OF TECHNICAL EVALUATION REPORT

(PUBLIC ASSESSMENT REPORT)

Cholera Vaccine (Inactivated, Oral)

M/s Bharat Biotech International Limited

Sy. No. 230, 231 & 235, Genome Valley, Turkapally, Shamirpet Mandal, Medchal-Malkajgiri District, Telangana State, India-500078

1. **Generic Name:**
   Cholera Vaccine (Inactivated, Oral)

2. **Description & Dosage Form:**
   Description: Uniform, turbid brownish suspension free of aggregates and extraneous particles.
   Dosage Form: Liquid vaccine.

3. **Presentations approved:**
   1.5 mL in respule (single dose)

4. **Composition (components and its quantity per dose):**

Each dose of 1.5 mL contains:	
Name of the ingredient	**Quantity**
Active Ingredient: V. cholerae (O1 El Tor Hikojima Serotype recombinant strain) formaldehyde inactivated whole cell	≥ 900 µg of LPS
Inactive Ingredient: Phosphate buffered saline	q.s. to 1.5 ml

5. **Approved Indication of the vaccine:**
   For active immunization against Diarrohoeal infection caused by Vibrio cholerae to children, adolescents and adults aged 1 year and above with two doses on Day 0 and Day 14.

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6. Posology of vaccine:

Two doses of 1.5mL of Hillchol® are administered orally with an interval of two weeks (doses on Day 0 and Day 14).

7. Instructions for administration:

The vaccine should be administered to anyone above the age of 1 year. 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 water (particularly to children) after administering the vaccine. 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.

8. Handling of multi dose vials:

Not Applicable

9. Concomitant medication (If any):

Not Applicable

10. Precautions for use:

Like all other vaccines, supervision and appropriate medical treatment should always be available to treat any anaphylactic reactions following immunization. Vaccines 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.

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11. Storage conditions:

+ 2°C to + 8°C

12. Shelf life approved:

24 months when stored at + 2°C to + 8°C.

13. Precautions for storage (If any):

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 respule in approved biological waste containers according to local regulations.

14. Brief description on container closure of drug product:

2.0 mL respule.

15. Regulatory Status in India and other Countries:

Not approved in other country.

16. The country of origin of imported product, responsible NRA and address (not applicable for indigenous vaccine):

Not applicable

17. Brief summary and conclusion of safety & immunogenicity/efficacy of Phase I, II and III clinical trials separately:

A) Phase I / II Clinical Trial:

A phase I/II 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 May2017.

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 received Hillchol® (high dose vaccine), Hillchol® (low dose vaccine) and Shanchol™ (comparator vaccine). The study was conducted in three age descending cohorts consisting of 360 participants of age 18 - 45 years (adults), 240 participants of age 5 - 17 years (older children) and 240 participants of age 1 - <5 years (younger children).

No significant safety events and adverse effects were observed in either formulation of test vaccine Hillchol® or the comparator vaccine recipients. The total occurrence rate of adverse events and adverse drug reactions was similar in both formulations of test and comparator groups. The Hillchol® low dose formulation (not less than 600 ug /ml) was found to be inferior in terms of immunogenicity to both Shanchol™ and to Hillchol® high dose formulation. It has been confirmed that the test vaccine Hillchol® high dose is non-inferior to the comparator vaccine in the primary efficacy endpoint, both in terms of seroconversion response and GMT for both Ogawa and Inaba serotype.

B) Phase III Clinical trial in India:

A phase III 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 10 approved clinical trial sites in India.

A total of 1800 participants in 3 age groups: Group 1: age ≥ 18 years, Group 2: age ≥ 5 to < 18 years and Group 3: age ≥ 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.

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 Hillchol® (BBV131) was demonstrated to be non-inferior to Shanchol for immunogenicity based on the seroconversion rates (defined as '4-fold rise in vibriocidal antibody titer compared to baseline') against Ogawa and Inaba serotypes, following 14 days of 2 doses of the vaccines across all age groups (≥1 to < 5 years, ≥5 to < 18 years and 18 years) and overall vaccine arms. The overall point estimate for the difference in seroconversion rates between the two vaccine arms was 0.32% [95% CI: - 4.6%, 5.4%], for Ogawa serotype and 2.03% [95% CI: - 2.8%, 7.1%] for Inaba serotype, thus the non-inferiority criterion for immunogenicity *lower bound 95% CI -10%* was considered achieved for the study.

A lot-to-lot consistency for Hillchol® (BBV131) immune response was demonstrated based on comparable anti-Ogawa and anti-Inaba serotype antibody titres across all 3 Lots. 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 overall adverse event profile (including solicited and unsolicited events) was well balanced and comparable between Hillchol® (BBV131) and Shanchol arms for all the study age groups.

18. Brief summary of review process of dossier (CTD format, CMC, CDL, SEC, GMP conclusions etc.):

The firm has submitted the New Drugs application through SUGAM online portal system in CTD format (Module-I, II, III,IV & V) for grant of permission to manufacture Cholera Vaccine (Inactivated, Oral) Drug product for sale or for distribution in 2 mL

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respules which includes manufacturing, testing, process validation & stability data of drug substance [Real time (2°C-8°C), accelerated (25 ± 2°C) and stress conditions (37±2°C)]and drug product [Real time (2°C - 8°C), accelerated (25±2°C) and stress conditions (37±2°C)], non-clinical data, Phase I/II clinical trial report of Dhaka, Bangladesh along with Phase III clinical trial report in Indian subjects.

Based on the documents/information submitted by the firm & review of the CMC (DS & DP) data along with the recommendations of SEC-Vaccine dated 27.03.2024 and comments of CDL, Kasauli on dossiers and three batches test reports from CDL, Kasauli the benefit-risk evaluation of proposed Cholera Vaccine (Inactivated, Oral) was considered favourable for grant of permission in Form CT-23 to the applicant, M/s Bharat Biotech International Limited Address: Sy. No. 230, 231 & 235, Genome Valley, Turkapally, Shamirpet Mandal, Medchal-Malkajgiri District, Telangana, India to manufacture Cholera Vaccine (Inactivated, Oral) as suspension for oral administration in single dose (1.5 mL) respules with the shelf life of 24 months when stored at + 2°C to + 8°C for active immunization against Diarrohoeal infection caused by Vibrio cholerae to the children, adolescents and adults aged 1 year and above with two doses on Day 0 and Day 14.