

Corporate Factsheet: Hillchol® (BBV131) - Next-Generation Oral Cholera Vaccine

Hillchol® (BBV131) is a revolutionary breakthrough in the global battle against cholera! This innovative vaccine offers a safe and potent method to address the growing demand for Oral Cholera Vaccines. Developed through extensive scientific collaboration and supported by thorough clinical trials, Hillchol® is dedicated to significantly reducing the worldwide cholera burden and improving public health outcomes on a global level.

Product Overview

- Name: Hillchol® (BBV131)
- Type: Novel Single Strain Oral Cholera Vaccine (OCV)
- Manufacturer: Bharat Biotech International Limited, in collaboration with MSD-Wellcome Trust and Hilleman Laboratories
- Active Ingredient: *V. cholerae* (O1 El Tor Hikojima Serotype recombinant strain) formaldehyde Inactivated Whole Cell
- Antigen Concentration: ≥ 900 mcg of LPS per dose
- Dosage Form: Single dose in respule, 1.5 mL per oral dose
- Dosage Administration: Orally administered on Day 0 and Day 14
- Target Population: Individuals aged > 1 year
- Storage: Store between $+2^{\circ}\text{C}$ and $+8^{\circ}\text{C}$

Key Features and Benefits

- **Effective Protection:** Provides robust immunity against cholera, reducing disease incidence and severity.
- **Easy Administration:** Oral delivery makes it user-friendly and ideal for mass immunization campaigns.
- **Wide Age Range:** Suitable for children and adults, enhancing community-wide protection.
- **Convenient Packaging:** Single-dose respules ensure accuracy and ease of use.
- **One-Component Formulation:** The Hillchol OCV (Oral Cholera Vaccine) is a single-component vaccine, making it simpler and more ease manufacturing than previous WHO prequalified vaccines. This streamlined approach aids in expanded scale production without compromising efficacy.
- **Engineered Strain for Better Immunogenicity:** Utilizes a formalin-inactivated *V. cholerae* O1 El Tor strain, engineered into serotype Hikojima. This engineering ensures the stable expression of both Ogawa and Inaba O1 lipopolysaccharide (LPS) antigens on the bacterial surface, optimizing the immune response.
- **Robust Antigen Expression:** The expression and immunogenicity of the LPS antigens—critical for the vaccine's effectiveness—are maintained, ensuring the vaccine's reliability and robust immune response.
- **Ease-Manufacturing:** By simplifying the vaccine to a single component and removing unnecessary elements, the Hillchol OCV can be manufactured efficiently and in bulk. This makes it more accessible and allows for broader distribution, especially in regions most affected by cholera.

- **Innovative Engineering:** The vaccine's development included the partial inactivation of the wbeT gene in the V. cholerae strain, a novel approach that ensures the co-expression of Ogawa and Inaba LPS antigens, enhancing the vaccine's protective capabilities.
- **Proven Foundation:** The concept behind the Hillchol vaccine, including the use of a formalin-inactivated Hikojima serotype V. cholerae strain, is grounded in research and findings published by Lebens et al. in 2011, signifying a solid scientific foundation for the vaccine's efficacy and safety.
- **Licensed and Developed for Global Use:** After licensing to Hilleman and subsequent development and testing in collaboration with BBIL, the optimized vaccine strain now used in Hillchol OCV demonstrates a worldwide commitment to combating cholera effectively.
- **Respule Presentation:** Transition to respules instead of glass vials for vaccine presentation offers improved storage efficiency, enhanced transport safety, and increased accessibility and convenience for single-dose applications. These contribute to a more efficient and safer vaccination process overall.

This vaccine represents a significant advancement in the global fight against cholera, offering a feasible, effective, and accessible option for cholera prevention, particularly in endemic regions.

Global Burden of Cholera

- Cholera is caused by Vibrio cholerae, impacting millions annually.
- In 2022, cholera outbreaks were reported in over 29 countries, with significant incidences in Africa and the Eastern Mediterranean.
- Approximately 2.9 million cases and 95,000 deaths occur annually worldwide.
- **Annual Incidence:** Estimates suggest that cholera affects 1.3 to 4.0 million people globally every year.
- **Mortality Rate:** The disease results in approximately 21,000 to 143,000 deaths worldwide annually.
- **Geographical Spread:** Cholera outbreaks are prevalent in developing countries across Africa, Asia, and the Americas, in both endemic and epidemic forms.
- **Recent Trends:** The number of cases reported to the World Health Organization (WHO) in 2022 more than doubled compared to 2021.
- In 2022, 44 countries reported cholera cases, up 25% from the 35 countries that reported in 2021. The year 2022 saw a significant surge in outbreaks, with 473,000 reported cases—double the previous year's figures.
- **Current Challenge:** As of March 2024, there have been 824,479 reported cases and 5,900 deaths, indicating a continuing challenge in controlling the disease. The efforts to eliminate cholera are being hampered by increasing cases and vaccine shortages.

Market Demand and Supply

- Estimated global demand for Oral Cholera Vaccines (OCVs) exceeds 100 million doses per year.
- India's demand is projected to rise from 20 million doses in 2021 to 80 million doses annually from 2024-2028.
- Critical imbalance in the market demand and supply dynamics of Oral Cholera Vaccines (OCV). Since January 2023, 17 countries have requested 102 million doses of OCV but

only 51 million doses produced during the same period, showcasing a significant supply-demand gap.

- Meeting the increasing global demand and effectively managing ongoing cholera outbreaks through strategic improvements in production and distribution, Bharat Biotech's entry aims to bridge the critical shortage gap of OCVs in India.
- The scalability and logistical benefits of Hillchol also highlight its crucial role in addressing the global demand for cholera vaccines in endemic and high-risk areas.

Development and Collaboration

- Hillchol[®]'s development involved collaboration between Hilleman Laboratories, the University of Gothenburg, Gotovax AB, and Bharat Biotech International Ltd. (BBIL), resulting in a scalable, single-antigen OCV
- Hillchol[®] was developed by Bharat Biotech after licensing from Hilleman Laboratories (funded by Merck, USA and Wellcome Trust, UK).
- Pre-clinical toxicology and Phase I/II, Phase III clinical studies demonstrate safety and immunogenicity.
- Studies published in peer-reviewed journals confirm efficacy and safety profile.

Development Highlights of the Hillchol OCV

Innovative Single-Component Vaccine: Hillchol OCV, features a single-component design that enhances ease and efficiency in manufacturing. Its use of a specifically engineered V. cholerae O1 El Tor strain delivers effective protection against cholera by expressing both Ogawa and Inaba O1 antigens.

Strategic Simplification Based on Research: Research initiated in 2009/10 led to significant simplification of the Hillchol OCV, focusing on key protective antigens and demonstrating that its efficacy is not compromised by the bacterial inactivation method.

First-of-its-Kind Engineering: The vaccine's breakthrough is its genetically engineered V. cholerae, expressing both essential LPS antigens, enabling the production of an optimized, easily manufacturable, and affordable whole-cell OCV.

Preclinical and Clinical Validation: The preclinical development journey and subsequent clinical trials underscore the safety and immunogenicity of the Hillchol OCV. Comprehensive studies, including toxicity assessments in rats and mice and oral immunization comparisons, have validated that the Hillchol OCV is as immunogenic as the comparator vaccine utilized in these studies, with similar antibody responses. Furthermore, a multi-stage clinical evaluation process, culminating in a Phase III study, confirmed the vaccine's non-inferiority to existing OCVs, establishing its potential for widespread public health use.

Licensing and Commercialization: After rigorous development and testing, the vaccine strain was licensed to Hilleman, with further licensing to BBIL, where it underwent additional

development. This resulted in commercial-scale production, meeting all expression and potency specifications, confirming Hillchol OCV as an effective global cholera prevention solution.

Public Health Impact:

- Hillchol® plays a critical role in controlling cholera outbreaks, particularly in regions with limited access to clean water and sanitation.
- Its use in vaccination programs can significantly lower the incidence of cholera, contributing to healthier communities and reducing the burden on healthcare systems.

Future Prospects

- Support from the Global Task Force on Cholera Control (GTFCC) aims to reduce cholera deaths by 90% globally by 2030.
- Emphasis on integrating OCV with water and sanitation improvements for comprehensive cholera control.

Economic Impact

- Cholera imposes a significant economic burden, estimated at US \$2 billion annually, due to healthcare costs and lost productivity.