Unit: Technical Assessment Unit

Public assessment report for biological products

(Euvichol plus)

Administrative information:

Trade name of the medicinal product:	Euvichol-Plus, 1.5mL/dose
INN (or common name) of the active substance(s):	OCV (Oral Inactivated Cholera vaccine)
Manufacturer of the finished product	Eubiologics Co. LTD Basement, 1F, 2-4~2-6, 3-1~3-4 and 4-6 of 4-dong and outdoor cold storage room 3~8, 56 Soyanggang-ro, Chuncheon-si, Gangwon-do, 24232, Republic of Korea - REPUBLIC OF KOREA
Marketing Authorization holder	Eubiologics Co. LTD Basement, 1F, 2-4~2-6, 3-1~3-4 and 4-6 of 4-dong and outdoor cold storage room 3~8, 56 Soyanggang-ro, Chuncheon-si, Gangwon-do, 24232, Republic of Korea - REPUBLIC OF KOREA
Applied Indication(s):	Cholera Disease
Pharmaceutical form(s) and strength(s):	Suspension with a yellow to yellowish color/1.5mL/dose
Route of administration	orally
Type of registration (EMA/FDA – Local)	Imported (WHO prequalified vaccine)

List of abbreviations

OCV	Oral Cholera Vaccine
WC	Whole Cell
WFI	Water For Injection
USP	United States Pharmacopeia
COA	Certificate Of Analysis
TSE	Transmissible Spongiform Encephalopathy
BSE	Bovine Spongiform Encephalopathy
MCB	Master Cell Bank
Ph. Eur	European Pharmacopeia
TRS	Technical Report Series
LPS	Lipopolysaccharide

MA	Marketing authorization
GLP	Good Laboratory Practice
WHO	World Health Organization
CRE	Creatinine
GMTs	Geometric mean titers

Table of contents

1. **General introduction about the product including brief description of the AI, its mode of action and indications:**

Cholera is a rapidly dehydrating diarrheal disease, which is preventable and treatable. It has a disease case burden of 2.8 million and kills approximately 100,000 people each year. Prolonged and frequent outbreaks can be devastating and dramatically impact many countries throughout the Asian, African, and Hispaniola region.
Safe and effective oral cholera vaccines (OCV) have been available since the mid-1980s, but have not been widely used due to concerns over low vaccine production capacity and possible diversion of traditional control effort.
Euvichol-Plus is an Oral Cholera Vaccine (OCV) containing inactivated whole cell (WC) of Vibrio cholerae O1 and O139 as active ingredients. The strains of V. cholerae used for this OCV are O1 Inaba Cairo 48 , O1 Inaba Phil 6973 El Tor, O1 Ogawa Cairo 50 and O139.
The final formulated bulk is prepared by mixing of five bulks (drug substances) obtained through the culture of above-mentioned strains of V. cholerae with phosphate buffer and WFI (Water for Injection).

2. **Quality aspects:**

2..1 Introduction

As mentioned in the aforementioned section.

2..2 Drug Substance (Active ingredient)

- **General information**

Liquid preparation of oral inactivated cholera vaccine containing O1and O139 of inactivated Vibrio Cholera. Compendial and common names are also provided in this section.

-**Nomenclature**:

The nomenclature is provided as OCV (Oral Inactivated Cholera vaccine)

- **Manufacture, process controls and characterization:**

Manufacturer:

Eubiologics Co. LTD Basement, 1F, 2-4~2-6, 3-1~3-4 and 4-6 of 4-dong and outdoor cold storage room 3~8, 56 Soyanggang-ro, Chuncheon-si, Gangwon-do, 24232, Republic of Korea - REPUBLIC OF KOREA has the whole responsibilities for the production and quality assurance of Euvichol-Plus and is in charge of production of drug substance.

-**Description of Manufacturing Process and Process Controls.**

Flow Chart of Manufacturing Process and Process Control is provided describes the main steps of manufacturing process, which are culture, recovery, inactivation and storage.

The composition feed media and Cholera growth media used for culture of Vibro Cholera strains and the manufacturing of drug substance for Euvichol-plus are provided.

Control of Materials

List of raw materials is provided including function, process step and reference. All materials comply either with European pharmacopeia, USP or with in-house specifications. COAs from EuBiologics and the suppliers for raw materials are provided.
TSE/BSE free certificate of casein is provided.

-Controls of Critical Steps and Intermediates.

Critical steps that affect the quality of the product are identified according to a risk assessment. Controls parameters of each critical step are listed include the process name, step, in process control and acceptance criteria. Analytical methods are provided.

- **Process Validation**

Process validation is conducted for 3 consecutive batches, report of process validation for drug substance is provided.

- **Manufacturing Process Development**

The history of development of manufacturing process is demonstrated starting from 2009 to 2017.
Assessment of history of development of manufacturing process and discuss impact on comparability (e.g. batches used for clinical trials vs commercial batches...).
Description of changes and reasons for changes (justification) with respect to the impact on quality, Critical assessment of the significance of changes and Control strategy development are provided and accepted.

- **Characterization**

Elucidation of structure and other characteristics is provided including summary of MCB characteristics and control tests according to standard operating procedures showing the characteristics of the drug substance. Moreover, Physical and chemical properties cannot be identified according to the nature of the drug substance which is polypeptides, instead biological characteristics can be analyzed.
Impurities are discussed and controlled.

- **Specification**

Table of specification is provided in tabular form including tests, acceptance criteria & method reference.

- **Analytical Procedures**

Analytical SOPs are attached.
In-house test methods are appearance; identification, purity and the rest are pharmacopeial.
Validation protocols and reports of the following analytical procedures are provided: identification, sterility, residual cholera toxin, free formaldehyde limit, and LPS assay.

- **Batch analysis**

Summary of batch analyses results and conformance to proposed specifications of inactivated DS are provided.

- **Reference Standards or Materials.**
  The reference standard used in testing of drug substance is provided.

- **Container closure system**
  The container closure system is described including type, name, model, manufacturer and specification.
  Method of sterilization is described to avoid protection from microbial contamination.

- **Stability of drug substance**

Based on available stability data,
approved Shelf Life: 24 months
approved Storage Conditions: 2-8 °C

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**

Euvichol-Plus is an oral cholera vaccine containing inactivated whole cell (WC) of Vibrio cholerae O1 and O139. Four strains of V. cholera are used which are O1 Inaba Cairo 48 , O1 Inaba Phil 6973 El Tor , O1 Ogawa Cairo 50 and O139. The final bulk is prepared by mixing of the five bulks fermentation of strains of V. cholerae with phosphate buffer and water for injection.
The composition with the formula amount and percentages of each component is presented clearly in a table form. 2 ml plastic tube final container is filled with 1.6 mL of the final formulated bulk solution (suspension with a yellow to yellowish color).

- Pharmaceutical Development including brief description on Components of drug product.

Methods of preparation, the chemical and biological characteristics of all four stains of V. cholerae are mentioned.
The phosphate buffered solution is used as an isotonic and pH control agent to maintain the pH in the range.

- Formulation Development

According to the provided file Euvichol-Plus is manufactured on the basis of the technology transferred by International Vaccine Institute (IVI), Korea. In order to meet the demand of this vaccine, in 2010. In (glass vial presentation) Euvichol® is formulated as an oral suspension of whole cell V. The production capacity of DS was increased.

- Overages: NA

- Physicochemical and Biological Properties

It is a suspension composed of inactivated WC V. cholerae, which often forms a precipitate; the precipitate can be converted to a suspension again by shaking the plastic tube.

Manufacturer:

- **Manufacture of the drug product:**

The production and quality assurance and is in charge of production of drug substance and final formulated bulk, filling, packaging and QC tests, the whole responsibilities are for Eubiologics Co. LTD Basement, 1F, 2-4~2-6, 3-1~3-4 and 4-6 of 4-dong and outdoor cold storage room 3~8, 56 Soyanggang-ro, Chuncheon-si, Gangwon-do, 24232, Republic of Korea - REPUBLIC OF KOREA.

- Description of manufacturing process and process controls along with manufacturers and responsibilities

A flow diagram for the manufacturing process is presented. Critical process parameters and critical quality attributes are indicated on the diagram. Detailed description of the manufacturing process is provided as following: preparation of final formulated bulk, filling and sealing then inspection and QC testing for Half-finished Products finally labeling and packaging. All stages are described in details.

- Control of critical steps and intermediates

In-process controls involved in manufacturing and their acceptance criteria are listed as follows: In- process and Quality Control test of Preparation of Final Formulated Bulk, test of Filling and Sealing, Leak test and Inkjet Printing, inspection, half-finished Products, addition to labeling and packaging

- Process validation and / or evaluation.

Validation protocol is established, process validation is conducted through the whole manufacturing stages: scale-up, aseptic process, time Out of Refrigerator, packaging and Shipping. Three (3) consecutive lots were used. Test results are within the acceptable criterion. It is verified that the designed production process could produce the product with consistent quality.

Product specification:

- It is established on the basis of WHO Guidelines for the Production & Control of Inactivated Oral Cholera Vaccines (TRS No. 924, 2004) and Oral Cholera Vaccine monograph of European Pharmacopeia.
- Table of specification is provided including tests, acceptance criteria & method references.

- The specification of appearance, identification, purity, residual Cholera toxin, and LPS content, are in house, while that of extractable volume is Korean Pharmacopoeia.

- Analytical procedures and SOPs details are provided. Validation reports of the analytical procedures are provided.

- Excipients are tested according to the guidelines of European Pharmacopoeia.
- Excipients are compendial and their analytical procedures are described in the Ph. Eur.
- None of the excipients are derived from human or animal origin.

- **Characterization of impurities**.
- Details on the characterization of impurities are provided.

- **Reference Standards or Materials.**

- The reference standards of cholera toxin, formaldehyde and Vibrio cholerae antibodies and the antigen standard used for the determination of LPS content are included, these standards are obtained from the registered suppliers except Vibrio cholerae O139 4260B antibody and LPS antigens are prepared by an in- house manufacturing process.
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- **Container closure system.**

- Primary Packaging Materials are Plastic tubes, constructed of Low-Density Polyethylene, its specifications and diagram of a plastic tubes are given. Secondary Packaging material such as, label, carton and package insert, their drawing and the actual sample are included.

- **Stability of the drug product.**

-Based on available stability data,
approved Shelf Life: 24 months
approved Storage Conditions: 2-8 °C

Adventitious agents

There is no material derived directly from biologicals among all the materials that were used in the production of Euvichol-Plus. However, some materials used in the culture of drug substance are extracted, synthesized or hydrolyzed from biological starting materials. A list of biological starting materials and their manufacturing methods are summarized in MA file.

3. Non –clinical aspect:

Euvichol Plus is an Oral Cholera Vaccine containing inactivated whole cell of Vibrio cholerae O1 and O139 as active ingredients. Vibrio cholerae is strictly a human pathogen and it doesn't colonize or replicate in healthy adult animals making it difficult to perform relevant non-clinical pharmacology and/or toxicology studies. Nevertheless, the applicant submitted a formal GLP toxicity

study that was performed to examine toxicological effects and potential target organs following repeat oral administration.

- **Pharmacology & pharmacokinetics:**
  Immunogenicity data in human were derived in clinical studies. Pharmacokinetics are not applicable for vaccines according to WHO guidelines on nonclinical evaluation of vaccines Annex 1 (TRS, No. 927, 2005**).**

- **Toxicology:**
  There were no critical findings related to mortality, clinical signs and/or change of body weight, water and food consumption, with the exception of: (1) a significant ($p < 0.05$) decrease in weight gain and the fasting weight at necropsy in the male treatment group, and (2) a reduction in the consumption of food and water in the female treatment group at Week 4. Considering safety laboratory tests, including urinalysis, hematology test and clinical biochemistry, there were no significant changes in various parameters with the exception of (1) significant ($p < 0.01$) increases in hemoglobin and hematocrit in the male treatment group, and (2) significant ($p < 0.05$) decrease of CRE in female treatment group. There were no meaningful changes in organ weights, and no adverse findings at necropsy or following histopathological examination.

- **Overall conclusion:** Based on the pharmacology and the toxicology data, Euvichol Plus is considered acceptable from the preclinical point of view.

4. **Clinical aspect:**

- **Clinical Efficacy (Immunogenicity):**
  A Phase III-UBC301, pivotal study demonstrated that Euvichol is immunologically non-inferior to Shanchol in generating protective responses against cholera. The efficacy analysis demonstrated that Euvichol achieved non-inferiority to Shanchol regarding seroconversion rates for the Ogawa O1 and Inaba O1 serotypes. Age stratified analyses further confirmed these findings, reinforcing Euvichol's efficacy as comparable to Shanchol.
  The GMT for the Ogawa serotype showed a statistically significant difference between the test group (Euvichol) and the comparator group (Shanchol), with higher results observed in the Euvichol group and there was no statistically significant difference in the Inaba serotype.
  However, the seroconversion rate for the O139 strain of Euvichol showed a statistically significant difference compared to Shanchol, indicating that noninferiority was not achieved. The vibriocidal response for O139 in vaccines is significantly lower than that for O1, due to the presence of the O139 capsule,

which may interfere with vaccine-induced immune responses or the detection of vibriocidal antibodies.

- **Clinical Safety:**

  A phase III- UBC301, Pivotal study comparative study evaluating the safety of Euvichol and Shanchol across 628 subjects reported a low incidence of adverse events (AEs), most of which were mild in intensity and resolved during the study period. 37 Solicited AEs occurred in 29 subjects (4.6%) in the Euvichol group and 59 solicited AE in 44 subjects (7%) in the Shanchol group, with headache being the most common symptom. Unsolicited AEs were slightly more frequent, with 92 cases in the Euvichol group and 104 in the Shanchol group. Common unsolicited events included headache, cough, nasopharyngitis, and pyrexia. No serious adverse events were observed, and there were no clinically significant differences in vital signs, lab results, or physical exams between the two groups, confirming a favorable safety profile for both vaccines.

  A comprehensive safety study involving 2,999 participants who received two doses of Euvichol found the vaccine to be well-tolerated, with most adverse events (AEs) being mild and resolving during the study period. Solicited AEs were reported in 147 subjects (4.9%), with headache being the most common (2.77%), followed by fever (1.47%), diarrhea (0.80%), and nausea/vomiting (0.43%). Unsolicited AEs occurred in 13.6% of subjects, with nasopharyngitis, cough, pyrexia, and headache being the most frequent. Only five events two solicited and three unsolicited were considered possibly related to the vaccine. No serious adverse events or deaths were reported, and no clinically significant changes were observed in vital signs, lab results, or physical exams. Phase I data also confirmed a favorable safety profile, with no serious adverse events among the 20 participants.

- **Overall conclusion:**

  Finally, the seroconversion rates for both O1 Ogawa and Inaba serotypes exceeded the non-inferiority threshold across all age groups, with Euvichol showing slightly higher efficacy. Geometric mean titers (GMTs) for Ogawa were significantly higher in the Euvichol group, while Inaba showed comparable results. Although Euvichol did not meet non-inferiority criteria for the O139 serotype, this outcome aligns with historically low immune responses due to the strain's capsule structure. Importantly, maternal vaccination with Euvichol may offer early protection for infants under six months, who are not eligible for direct immunization.

  The safety profile of Euvichol is deemed acceptable, as no clinically significant safety issues were identified in the Euvichol group compared to the Shanchol group.

- **Benefit/ Risk discussion:**

  In conclusion the overall benefit/risk of Euvichol is favourable in Prevention of Cholera caused by Vibrio cholerae but the efficacy against Vibrio cholerae serogroup 0139 was not demonstrated.

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.