SUMMARY OF PRODUCT CHARACTERISTICS

Euvichol-Plus (Oral Cholera Vaccine)

1. NAME OF THE MEDICINAL PRODUCT

Euvichol-Plus (Inactivated Oral Cholera Vaccine containing O1 and O139 of *Vibrio cholerae)*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (1.5 mL) contains:

	Amount
Active Ingredients:	
Vibrio cholerae O1 Inaba Cairo 48 classical biotype, (Heat inactivated)	300 L.E.U.*
Vibrio cholerae O1 Inaba Phil 6973 El Tor biotype, (Formalin inactivated)	600 L.E.U.
Vibrio cholerae O1 Ogawa Cairo 50 classical biotype, (Formalin inactivated)	300 L.E.U.
Vibrio cholerae O1 Ogawa Cairo 50 classical biotype, (Heat inactivated)	300 L.E.U.
Vibrio cholerae O139 4260B (Formalin inactivated)	600 L.E.U.
Excipients:	
Sodium phosphate dibasic dihydrate	4.68 mg
Sodium phosphate monobasic dihydrate	0.97 mg
Sodium chloride	12.75 mg
Water for injection	q.s to 1.5mL

*L.E. U: Lipopolysaccharide ELISA Units

3. PHARMACEUTICAL FORM

Liquid formulation of Oral Cholera Vaccine

4. CLINICAL PARTICULARS

4. 1. Therapeutic indications

The vaccine should be administered to individuals aged 1 year and above for the prevention of Cholera caused by *Vibrio cholerae*.

4. 2. Posology and method of administration Posology

A single 1.5 mL dose of Euvichol-Plus is recommended.

Method of administration

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. Take a sip of water if necessary. The frozen vaccines should not be taken. The vaccine should not be administered parenterally (intramuscularly, subcutaneously or intravenously). The vaccine is only recommended for oral administration.

4. 3. Contraindications

1. 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 due to the previously taken dose.
2. Immunization with Euvichol-Plus 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

1. As with any vaccine, immunization with Euvichol-Plus may not protect 100% of susceptible persons.
2. 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 person should remain under medical supervision for at least 30 minutes after vaccination.

3. This vaccine contains residual formaldehyde. Caution should be taken in subjects with known hypersensitivity to formaldehyde.
4. The safety and immune response of Euvichol-Plus has not been clinically evaluated in individual with HIV/AIDS.
5. No specific clinical study has been conducted to evaluate the efficacy and safety of Euvichol-Plus in pregnant and lactation women. Therefore, the vaccine is not recommended for use in pregnancy.
6. No clinical study has been performed to evaluate the efficacy and safety of Euvichol-Plus in infants (less than 1 year of age). Therefore, the vaccine is not recommended for use in infants.

4. 5. Interaction with other medicinal products and other forms of interaction

Not applicable

4. 6. Pregnancy and lactation

Not applicable

4. 7. Effects on ability to drive and use machines

Not applicable

4. 8. Undesirable effects

2,999 healthy children and adults (1-40 years) participated in the clinical study for evaluating safety.

1. After taking the vaccines, during the first 7 days, the most frequently reported adverse drug reactions in the clinical trial were headache, fever, diarrhea, Nausea/Vomiting and Myalgia and 102 subjects (3.40%) among 2,999 subjects were reported. The incidence rate for children and adults was described on the table below.

	Total (N=2999)	1~17 years (N=1118)	18~40 years (N=1881)

Total	3.40%	3.04%	3.62%
Headache	1.83%	0.81%	2.45%
Fever	1.00%	1.97%	0.43%
Diarrhea	0.67%	0.54%	0.74%
Nausea/Vomiting	0.37%	0.63%	0.21%
Myalgia	0.10%	0.00%	0.16%

2. After taking the vaccines, adverse drug reactions were examined for a period of 28 days. 69 subjects (2.30%) among 2,999 subjects were reported with the adverse effects, and Gastrointestinal disorders were reported the highest numbers i.e., 35 subjects (1.17%). The adverse drug reactions during the study (28 days) were described on the table below. (Uncommon: 0.1~5%, Rare: less than 0.1%)

	Incidence rate	
	Uncommon	Rare
Gastrointestinal disorders	Abdominal pain, toothache diarrhea	Vomiting, abdominal pain
General disorders and administration site condition	Pyrexia	Thirst
Infection and infestations	Nasopharyngitis	Gastroenteritis
Nervous system disorders	Headache	Dizziness
Respiratory, thoracic and meditational disorders	Cough	Orpharyngeal pain
Skin and subcutaneous tissue disorders	Pruritus	Rash macular
Musculoskeletal and connective tissue disorders	-	Arthralgia, neck pain, pain in extremity

Vascular disorders	-	Flushing

3. Serious adverse event did not occur during the clinical trial period.

4. 9. Overdose

Not applicable

5. PHARMACOLOGICAL PROPERTIES

5. 1. Pharmacodynamic properties

Although the Note for Guidance (NFG) states that the pharmacodynamic studies of any biological drugs "should be carried out" in "appropriate animal models", there is no valid model available in order to predict the mucosal immune responses in animals after the administration of an Oral Cholera Vaccine (OCV). It has also been mentioned that inactivated Gram-negative bacteria are not immunogenic to animals, not even in monkeys, while they are administrated orally. In addition, no potency or immunogenicity assay has been recommended to conduct in animals that could be used as a reliable indicator of protective efficacy of the inactivated OCVs in humans. For this reason, an animal potency assay has been omitted from the WHO Guidelines for the production and control of inactivated oral cholera vaccines. On the basis of these considerations, and because of the nature of the vaccine (inactivated whole cells), mode of administration (oral), and the lack of the requirement by multiple competent regulatory authorities and WHO to conduct any further nonclinical toxicity testing, formal developmental toxicity studies have not been conducted by other marketed OCVs (Dukoral® and ShancholTM).

5. 2. Pharmacokinetic properties

Pharmacokinetic studies of Euvichol® were not conducted as there is no valid animal model to do so. Pharmacokinetic studies of OCV have not been recommended as this vaccine is taken orally and the components of OCV are not systemically absorbed in the intestine. Moreover, it is observed that PK/PD studies have not been conducted in the case of other marketed OCVs (i.e., Dukoral® and ShancholTM).

5. 3. Preclinical safety data

A formal toxicity study of Euvichol was performed to examine toxicological effects and potential target organs following repeat oral administration to Sprague-Dawley rats for 6 weeks (3 times, once every 2 weeks ["N+1" design]) to further establish its safety for human administration. The study was conducted in accordance with the guidelines established for Good Laboratory Practice (GLP) principles of the Korea Food and Drug Administration (Guidance 2009-183, December 22, 2009) and the Organization for Economic Co-operation and Development (OECD) (1997).

Test vaccine or placebo was administered to female and male Sprague-Dawley rats at the full human dose (1.5 mL) by oral gavage. Test parameters included changes in clinical signs, body weights, food and water consumption, urinalysis, hematological and clinical biochemistry tests, organ weights, necropsy and macro-and histopathological examination. 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. In 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.

6. PHARMACEUTICAL PARTICULARS

6. 1. List of excipients

Sodium phosphate dibasic dihydrate

Sodium phosphate monobasic dihydrate

Sodium chloride

Water for injection

6. 2. Incompatibilities

Not applicable

6. 3. Shelf life

The vaccine should be stored at 2℃ ~ 8℃. Do not freeze. The expiry date of the vaccine is 24 months from the date of manufacture.

6. 4. Special precautions for storage

Not applicable

6. 5. Nature and contents of container

The Plastic tubes are constructed of LDPE (Low Density Polyethylene) are tested for the compliance with Ph. Eur. Euvichol-Plus is over-filled (1.6 mL per tube) in order to assure that the recommended dose (1.5 mL) must be administered since a minute amount of suspension might remain in the tube even after the vaccination.

6. 6. Special precautions for use, handling and disposal

Not applicable

7. MARKETING AUTHORISATION HOLDER

Techinvention Lifecare Pvt. Ltd.

8. MARKETING AUTHORISATION NUMBER(S)

IMP/BIO/23/000044

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17th April 2023

10. DATE OF REVISION OF THE TEXT

20th September 2023