SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Euvichol-Plus

2. QUALITAVTIVE AND QUANTITATIVE COMPOSITION

One dose (1.5 mL) contains:

Active ingredients:

V. cholerae O1 Inaba Cairo 48 classical biotype, Heat inactivated ····· 300 L.E.U*
V. cholerae O1 Inaba Phil 6973 El Tor biotype, Formalin inactivated ····· 600 L.E.U
V. cholerae O1 Ogawa Cairo 50 classical biotype, Formalin inactivated ····· 300 L.E.U
V. cholerae O1 Ogawa Cairo 50 classical biotype, Heat inactivated ····· 300 L.E.U
V. cholerae O139 4260B, Formalin inactivated ····· 600 L.E.U
*L.E.U: Lipopolysaccharide ELISA Units

Excipients:
Buffer solution
For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

1 dose (2mL plastic tube) contains 1.5mL of suspensions.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of Cholera caused by *Vibrio cholerae* but the efficacy against *Vibrio cholerae* serogroup O139 was not demonstrated.

4.2 Posology and method of administration

① The vaccine should be administered to anyone above the age of 1 year.

② Two doses of vaccine should be given at an interval of two weeks.

③ The vaccine is presented as a suspension. Therefore, after shaking the vaccine vial rigorously, 1.5 mL of the vaccine should be squirted into the mouth. Take a sip of water if necessary.

④ The frozen vaccines should not be taken.

⑤ 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 studies have 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 studies have 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

Appropriate studies have not been conducted to determine if drug interactions occur.

4.6 Pregnancy and lactation

The safety of the product during pregnancy and lactation has not been established. In the absence of sufficient data, use during pregnancy or lactation is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

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

① After taking the vaccines, during 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 is described on the table below.

	Total (N=2,999)	1 ~ 17 years (N=1,118)	18~40 years (N=1,881)
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 upper
General disorders and administration site condition	Pyrexia	Thirst
Infection and infestations	Nasopharyngitis	Gastroenteritis
Nervous system disorders	Headache	Dizziness

Respiratory, thoracic and mediastinal disorders	Cough	Oropharyngeal pain
Skin and subcutaneous tissue disorders	Pruritus	Rash macular
Musculoskeletal and connective tissue disorders	-	Arthralgia, neck pain, pain in extremity
Vascular disorders	-	Flushing

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Not required as per WHO Technical Report Series No. 924, 2004

5.2 Pharmacokinetic properties

Not required as per WHO Technical Report Series No. 924, 2004

5.3 Preclinical safety data

The active ingredients of Euvichol are unlikely to exhibit any toxicity to mammals. It has been reported that oral administration of inactivated Gram-negative bacteria is not likely to cause any toxicity to mammals [EMEA 2005]. Nevertheless, nonclinical (repeat-dose toxicity) study was performed to estimate the toxicity and to identify the target organ after repeated dose administration. A formal toxicity study of Euvichol was performed to examine toxicological effects and potential target organs following repeated 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.

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

Buffer Solution:

Sodium phosphate dibasic dihydrate

Sodium phosphate monobasic dehydrate

Sodium chloride

Water for injection

6.2 Incompatibilities

None Known

6.3 Shelf life

The expiry date of the vaccine is 24 months from the date of manufacture.

6.4 Special precautions for storage

The vaccine should be stored at 2°C ~ 8°C. Do not freeze.

6.5 **Nature and contents of container**

1.5 mL of the final formulated bulk of Euvichol-Plus is filled into a 2 mL of plastic tube (LDPE).

6.6 **Special precautions for disposal**

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

7. **MARKETING AUTHORISATION HOLDER**

EuBiologics Co., Ltd.
Basement, 1F, 2-4~6 and 3-1~4 of 4-dong, 56 Soyanggang-ro, Chuncheon-si, Gangwon-do, South Korea

8. **MARKETING AUTHORISATION NUMBER(S)**

H2024/CTD11328/24084

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorization: 29 March 2017

10. **DATE OF REVISION OF THE TEXT**

October 2017