NEW ZEALAND DATA SHEET

1 DUKORAL®

DUKORAL® is an oral vaccine containing heat-inactivated *Vibrio cholerae* O1 Inaba classic strain, formalin-inactivated *Vibrio cholerae* O1 Inaba El Tor strain, heat-inactivated *Vibrio cholerae* O1 Ogawa classic strain, formalin-inactivated *Vibrio cholerae* O1 Ogawa classic strain, and recombinant *Vibrio cholerae* toxin B subunit.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose contains:

Active ingredients

- A total of 1.25 x 10^{11} bacteria of the following strains:

Vibrio cholerae O1 Inaba classic strain, heat-inactivated	ca. 31.25 x 10^{9} bacteria*
Vibrio cholerae O1 Inaba El Tor strain, formalin-inactivated	ca. 31.25 x 10^{9} bacteria*
Vibrio cholerae O1 Ogawa classic strain, formalin-inactivated	ca. 31.25 x 10^{9} bacteria*
Vibrio cholerae O1 Ogawa classic strain, heat-inactivated	ca. 31.25 x 10^{9} bacteria*

*bacterial count before inactivation

- Recombinant cholera toxin B subunit 1 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

DUKORAL® is provided as a whitish oral liquid suspension (vaccine) in a single-dose glass vial with white to off-white effervescent powder (buffer), in an accompanying sachet.
The vaccine suspension is filled to a volume of 3 mL in vials (type I glass) with a rubber stopper (bromobutyl rubber) and a screw cap.
DUKORAL® is available in the following pack size:

Single-dose carton: one vaccine vial and one sachet of effervescent powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cholera: Active immunisation of adults and children *from 2 years of age,* who will be visiting areas with an ongoing or anticipated epidemic or who will be spending an extended period of time in areas in which cholera infection is a risk.
The vaccine should be considered for foreign aid workers and others intending to visit or spend an extended period of time in areas endemic or epidemic for cholera.
ETEC: Active immunisation of adults and children *from 2 years of age* who will be visiting areas posing a great risk of diarrhoeal illness caused by enterotoxigenic *Escherichia coli* (ETEC), one of the most common causes of "travellers' diarrhoea".
DUKORAL® should not replace standard protective measures. In the event of diarrhoea, measures of rehydration should be instituted.

4.2 Dose and method of administration

Dosage

Cholera:
Primary immunisation: Consists of two doses of vaccine for adults and children over the age of 6. Children from 2 to 6 years of age should receive three doses. Doses are to be administered at intervals of at least 1 week. **If more than 6 weeks elapse between doses, the primary immunisation course should be re-started**. Immunisation should be completed at least 1 week prior to potential exposure.
Booster dose: For optimum long-term protection, a single booster dose is recommended for adults

after 2 years. Children from 2 to 6 years of age should receive a booster dose after 6 months. No clinical efficacy data has been generated on repeat booster dosing.

ETEC:
Primary immunisation: Consists of two doses of vaccine for adults and children from 2 years of age. Doses are to be administered at an interval of at least 1 week. **If more than 6 weeks elapse between doses, the primary immunisation course should be re-started.**
Satisfactory protection against cholera and ETEC diarrhoea can be expected about 1 week after primary immunisation is concluded.

Booster dose: No specific interval can be recommended for booster doses for protection against ETEC, due to the lack of clinical data on booster dosing.

Administration
The vaccine is intended for oral use. Before ingestion, the vaccine suspension should be mixed with a buffer (sodium hydrogen carbonate) solution prepared from the supplied effervescent powder. Dissolve the effervescent powder in approximately 150 mL of cool water to make the buffer solution. Shake the vaccine vial gently and add the contents to the buffer solution. Mix well and drink the mixture.

Children 2 to 6 years of age: half the amount of buffer solution is poured away and the remaining part (approx. 75 mL) is mixed with the entire contents of the vaccine vial.

Food and drink should be avoided for 1 hour before and 1 hour after vaccine administration.
For administration with other oral medicinal products, see 'Interaction with other medicines and other forms of interaction'.

DUKORAL® should only be mixed with the supplied effervescent powder dissolved in water. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

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

4.3 Contraindications
Hypersensitivity to the active substances, to any of the excipients listed in section 6.1 or to formaldehyde.

Administration of DUKORAL® should be postponed for people suffering from acute gastrointestinal illness or acute febrile illness.

4.4 Special warnings and precautions for use
No clinical data on protective efficacy of DUKORAL® against cholera after administration of booster doses are available.

DUKORAL® confers protection specific to Vibrio cholerae serogroup O1. Immunisation does not protect against V. cholerae serogroup O139 or other species of Vibrio cholerae. The vaccine does not provide complete protection and it is important to adhere additionally to standard protective measures to avoid cholera.

In people infected with HIV, limited data are available on immunogenicity and safety of the vaccine. Vaccine protective efficacy has not been studied in these people. Immunisation of HIV-positive

people result in transient increases of viral load. DUKORAL® may not induce protective antibody levels in people with advanced HIV disease. However, an effectiveness study in a population with high HIV prevalence showed similar protection as in other populations.
Antibody response in vaccinees with endogenous or iatrogenic immunosuppression may be insufficient.

Formaldehyde is used during the manufacturing process, and trace amounts may be present in the final product. Caution should be taken in people with known hypersensitivity to formaldehyde.

DUKORAL® contains approximately 1.1 g sodium per dose, which should be taken into consideration by patients on a controlled sodium diet.

Paediatric population
DUKORAL® has been given to children between 1 and 2 years of age in safety and immunogenicity studies, but the protective efficacy has not been studied in this age group. Therefore, DUKORAL® is not recommended for use in children younger than 2 years of age.

Use in elderly patients
There are only very limited data on protective efficacy of the vaccine in people aged 65 years and over.

Carcinogenicity
DUKORAL® has not been evaluated for carcinogenicity.

Genotoxicity
DUKORAL® has not been evaluated for mutagenicity.

4.5 Interaction with other medicines and other forms of interaction

The vaccine is acid labile. Food and/or drink will increase acid production in the stomach, and the effect of the vaccine may be impaired. Consequently, food and drink should be avoided 1 hour before and 1 hour after vaccination.

Oral administration of other vaccines and medicinal products should be avoided 1 hour before and 1 hour after administration of DUKORAL®.

Preliminary results from a clinical study in a limited number of volunteers showed no interaction with the antibody response to DUKORAL® when a live oral vaccine (enterocapsules) against typhoid was given simultaneously with DUKORAL®. The immune response to live typhoid vaccine was not investigated in this study.

Similarly, a yellow fever vaccine was given concomitantly with DUKORAL®, and there was no interaction observed with the immune response to the yellow fever vaccine. The immune responses to DUKORAL® were not studied.

No other vaccines/medicinal products, including oral polio vaccine and antimalarials, have been given simultaneously with DUKORAL® in clinical studies.

Effects on laboratory tests have not been documented.

4.6 Fertility, pregnancy and lactation

No animal data on reproduction toxicity are available. Following careful benefit/risk assessment the

vaccine may be administered during pregnancy, although no specific studies have been conducted to investigate the safety of DUKORAL® during pregnancy. However, DUKORAL® is an inactivated, non-replicating vaccine given orally and it is not taken up by the blood stream. It is therefore considered to be safe.

During a mass-vaccination campaign conducted in Zanzibar, 196 mothers had received at least one dose of DUKORAL® during pregnancy. There was no statistically significant evidence of a harmful effect of DUKORAL® exposure during pregnancy.

Following careful benefit/risk assessment the vaccine may be administered to lactating women. It has been given to lactating women in several studies, although no specific studies have been conducted to investigate the safety of DUKORAL® during lactation.

DUKORAL® has not been evaluated for impairment of fertility.

4.7 Effects on ability to drive and use machines

There is no evidence of an effect on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions are adverse events that were considered to be reasonably associated with the use of DUKORAL® based on the comprehensive assessment of the available adverse event information. A causal relationship with DUKORAL® cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, rates of adverse reactions observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in clinical practice.

The safety of DUKORAL® was assessed in clinical trials, including both adults and children, conducted in endemic and non-endemic countries for cholera and enterotoxigenic *Escherichia coli* (ETEC) producing heat-labile enterotoxin (LT). Over 94,000 doses of DUKORAL® were administered during the clinical trials. Evaluation of safety varied between trials with respect to mode of surveillance, definition of symptoms and time of follow-up. In most of these studies adverse events were assessed by passive surveillance. The most frequently reported adverse reactions (such as gastrointestinal symptoms including abdominal pain, diarrhoea, loose stools, nausea and vomiting), occurred at similar frequencies in vaccine and placebo groups.

Frequency classification: Very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<u>Metabolism and nutrition disorder</u>

Rare: Loss of/or poor appetite
Very rare: Dehydration

<u>Nervous system disorders</u>

Uncommon: Headache
Rare: Dizziness
Very rare: Drowsiness, insomnia, fainting, reduced sense of taste

Respiratory, thoracic and mediastinal disorders
Rare: Respiratory symptoms (including rhinitis and cough)

Gastrointestinal disorders
Uncommon: Diarrhoea, abdominal cramps, abdominal pain, stomach/abdominal gurgling (gas), abdominal discomfort
Rare: Vomiting, nausea
Very rare: Sore throat, dyspepsia

Skin and subcutaneous tissue disorders
Very rare: Sweating, rash

Musculoskeletal and connective tissue disorders
Very rare: Joint pain

General disorders and administration site conditions
Rare: Fever, malaise
Very rare: Fatigue, shivers

Post-marketing data
Additional adverse reactions reported during post-marketing surveillance, are listed below. The frequency cannot be estimated from the available data.

Infections and infestations: Gastroenteritis
Blood and lymphatic system disorders: Lymphadenitis
Nervous system disorders: Paraesthesia
Vascular disorders: Hypertension
Respiratory, thoracic and mediastinal disorders: Dyspnoea, increased sputum
Gastrointestinal disorders: Flatulence
Skin and subcutaneous tissue disorders: Urticaria, angioedema, pruritus
General disorders and administration site conditions: Pain, flu-like syndrome, asthenia, chills

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose
Data on overdose are limited. Adverse reactions reported following overdose have been consistent with those seen after the recommended dosing.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
The vaccine contains killed whole *Vibrio cholerae* O1 bacteria and the recombinant non-toxic B-subunit of the cholera toxin (CTB). Bacterial strains of both Inaba and Ogawa serotypes and of El Tor and Classical biotypes are included in the vaccine. DUKORAL® is taken orally with bicarbonate

buffer, which protects the antigens from the gastric acid. The vaccine acts by inducing antibodies against both the bacterial components and CTB. The antibacterial intestinal antibodies prevent the bacteria from attaching to the intestinal wall, thereby impeding colonisation of *V. cholerae* O1. The anti-toxin intestinal antibodies prevent the cholera toxin from binding to the intestinal mucosal surface, thereby preventing the toxin-mediated diarrhoeal symptoms.
The heat-labile toxin (LT) of enterotoxigenic Escherichia coli (ETEC) is structurally, functionally and immunologically similar to CTB. The two toxins cross-react immunologically. This means that DUKORAL® also will protect against ETEC diarrhoea.

Cholera and ETEC infections are limited to the intestinal tract. Oral administration will induce local immunity.

Since the B-subunit is acid labile, the vaccine is mixed with a buffering sodium hydrogen carbonate solution.

Clinical Efficacy and Safety
Efficacy against cholera:
Clinical results have revealed a protective efficacy against cholera of 80–85% for the first six months in all age categories. In adults and children over the age of 6 years, protective efficacy over a 3-year follow-up period averaged about 63% (without a booster dose). Children under the age of 2 years were not examined, but protective efficacy in the 2–6-year age range was satisfactory for the first 6 months.

In an efficacy study including 89,596 adults and children aged 2 years and older in Bangladesh, the efficacy of DUKORAL® against cholera was 85% in the 6 months after the third dose and 57% in the second year after immunisation. Protective efficacy declined over the 3-year study period, declining more rapidly in those under 6 years of age.

An exploratory analysis suggested that two vaccine doses seemed as effective as three doses in adults.

Protective efficacy of DUKORAL® against cholera has not been studied following repeated booster vaccination.

Protective effectiveness against cholera was evaluated during two mass-vaccination campaigns conducted in Mozambique (December 2003 – January 2004) and Zanzibar (February 2009 – May 2010).

In the case-control study conducted during the mass vaccination campaign in Mozambique, protective effectiveness of two doses of DUKORAL® was 84% (95% CI: 43, 95, per-protocol analysis; p=0.005) for the initial 5 months of follow-up.

In the longitudinal cohort-analysis conducted during the mass-vaccination campaign in Zanzibar, protective effectiveness after two doses of DUKORAL® was 79% (95% CI, 47, 92) for a follow-up period of 15 months. In addition to the direct protection, it was shown that DUKORAL® provides significant indirect (herd) protection in the studied setting.

Efficacy against ETEC:
Protective efficacy against ETEC diarrhoea is about 60%. Protective efficacy with reference to all kinds of tourist diarrhoea will vary depending on the prevalence of ETEC. There are considerable variations between different seasons and geographic areas. Protective efficacy against ETEC is of

comparatively short duration, lasting about 3 months.

In a prospective double-blind clinical trial conducted in Finnish travellers, 615 healthy persons aged 15 years and older received two doses of either DUKORAL® (N = 307) or placebo (N = 308) before trip departure. The total incidence of diarrhoea, independent of cause, was 31% in the placebo treated group and 24% in the DUKORAL® treated group — i.e. 23% protective efficacy against all types of 'travellers' diarrhoea.

In a randomised, double-blind efficacy study done in Bangladesh in 89,596 adults and children aged 2 years and older, DUKORAL® conferred 67% protection against episodes of diarrhoea caused by enterotoxigenic *E. coli* synthesising heat-labile toxin (LT-ETEC) during the initial 3 months of follow-up but demonstrated no protection thereafter. Protective efficacy against clinically severe episodes of LT-ETEC was 86%.

5.2 Pharmacokinetic properties
Not applicable.

5.3 Preclinical safety data
No preclinical safety testing with the vaccine has been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Vaccine, 1 dose (3 mL) contains:

Sodium phosphate, monobasic dihydrate	1.95 mg
Sodium phosphate, dibasic dihydrate	9.39 mg
Sodium chloride	25.5 mg
Water for injections	to 3.0 mL
Effervescent powder, one sachet (5.6 g) contains:	
Sodium bicarbonate	3600 mg
Citric acid, anhydrous	1450 mg
Raspberry flavour	70.0 mg
Sodium carbonate anhydrous	400 mg
Sodium citrate	6.0 mg
Sodium saccharin	30.0 mg

6.2 Incompatibilities
In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life
3 years.
After the effervescent powder has been dissolved in water and the vaccine suspension has been added, the mixture should be drunk within 2 hours.

6.4 Special precautions for storage
Store at 2° to 8°C. REFRIGERATE. DO NOT FREEZE.
Do not use after expiry date.
For storage conditions after reconstitution of the medicine, see section 6.3.

6.5 Nature and contents of container

The vaccine suspension is filled in a volume of 3 mL in bottles (type I glass) with a rubber stopper (bromobutyl rubber) and a screw cap.
The effervescent powder is filled in an amount of 5.6 g in sachets with an inner layer of polyester/ low-density polyethylene and an outer layer of aluminium/LDPE.
Each dose of vaccine is supplied with one sachet of effervescent powder.
Each pack contains one dose.

6.6 Special precautions for disposal and other handling

The effervescent powder should be dissolved in approximately 150 mL of cool water. The vaccine bottle should be shaken gently and the vaccine suspension should then be added to the buffer solution and mixed well to obtain a colourless slightly opalescent solution.

Children 2 to 6 years of age: half of the buffer solution is poured away and the remaining part (approx. 75 mL) is mixed with the entire contents of the vaccine bottle.

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

7 MEDICINE SCHEDULE

Prescription Medicine, except when sold in a pharmacy by a registered pharmacist who is an authorised vaccinator.

8 SPONSOR

Seqirus (NZ) Ltd
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Auckland 1546
NEW ZEALAND
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9 DATE OF FIRST APPROVAL

28 February 2002

10 DATE OF REVISION OF THE TEXT

3 August 2020

DUKORAL® is a registered trademark of Valneva Sweden AB.

SUMMARY TABLE OF CHANGES

Section changed		Summary of new information
7	**MEDICINE SCHEDULE**	Update classification of Dukoral
10.	**DATE OF REVISION OF THE TEXT**	22 November 2019