AUSTRALIAN PRODUCT INFORMATION - DUKORAL®
[Vibrio cholerae]
ORAL LIQUID SUSPENSION

1 NAME OF THE MEDICINE

Vibrio cholerae

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

Each dose of vaccine suspension (3 ml) 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 1mg

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

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.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

DUKORAL® is indicated for use in the prevention of cholera caused by serogroup O1 *Vibrio cholerae*. DUKORAL® can be used for active immunisation of adults and children *from two years of age,* who will be visiting areas epidemic or endemic for cholera and who are at high risk of infection.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Primary immunisation consists of 2 doses for adults and children over the age of 6. Children from 2 to 6 years of age should receive 3 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.

Booster dose: For continuous protection against cholera a single booster dose is recommended within 2 years for adults and children from 6 years of age, and within 6 months for children aged 2 to below 6 years. No clinical efficacy data has been generated on repeat booster dosing. However, immunological and duration of protection data suggest that if up to 2 years have elapsed since the last vaccination for adults and children from 6 years of age, and up to 6 months for children aged 2 to below 6 years, a single booster dose should be given. If more than 2 years have elapsed since the last vaccination (more than 6 months for children aged 2 to below 6 years) the primary course should be repeated.

Satisfactory protection against cholera can be expected about two weeks after completing the primary immunisation course.

No clinical data on protective efficacy of DUKORAL® against cholera after administration of booster doses are available.

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.

Adults and children >6 years of age:

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:

After dissolving the effervescent powder in 150 mL of cool water, 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.

General considerations:

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

Food and drink should be avoided for 1 hour before and 1 hour after vaccine administration.

For administration with other oral medicinal products, see '**Interactions with other medicines**'.

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 or to formaldehyde.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

As with any vaccine, immunisation with DUKORAL® may not protect 100% of susceptible individuals. DUKORAL® confers protection specific to *Vibrio cholerae* serogroup O1. Immunisation with DUKORAL® does not protect against *V. cholerae* serogroup O139 or other species of *Vibrio cholerae*.

DUKORAL® is effective in providing protection against clinical cholera. DUKORAL® does not necessarily prevent the spread of cholera via a vaccinee exposed to *V. cholerae* bacteria.

Cholera vaccine is not a sole measure in prevention of cholera outbreaks and should be combined with good hygiene practices.

In subjects infected with HIV, limited data are available on immunogenicity and safety of DUKORAL®. Vaccine efficacy has not been assessed in these subjects. Immunisation of HIV infected subjects may result in transient increases of viral load. DUKORAL® may not induce protective antibody levels in subjects with advanced HIV disease.

The antibody response in DUKORAL® 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 subjects with known hypersensitivity to formaldehyde.

DUKORAL® contains approximately 1,200 mg sodium per dose, which should be taken into consideration for patients on a controlled sodium diet.

Use in the elderly

There are only very limited data on protective efficacy of the vaccine in subjects aged 65 years and over.

Paediatric use

DUKORAL® has been administered 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 to be used in children less than 2 years of age.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

DUKORAL® 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 medicinal products should also be avoided 1 hour before and 1 hour after administration of DUKORAL®.

Except for yellow fever vaccine, co-administration of DUKORAL® with other vaccines has not been sufficiently assessed in clinical studies. The administration of an encapsulated oral typhoid vaccine and DUKORAL® should be separated by at least 8 hours.

DUKORAL® has been administered concomitantly with yellow fever vaccine to 55 subjects. The yellow fever antibody response was similar to that seen in the 58 subjects who received the yellow fever vaccine alone. However, no results are available to evaluate the safety of concomitant administration of the two vaccines or to evaluate the immune response to DUKORAL® when administered with yellow fever vaccine.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

DUKORAL® has not been evaluated for impairment of fertility.

Use in pregnancy – Pregnancy Category B2

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.

Use in lactation

Following careful benefit/risk assessment DUKORAL® 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.

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 ADVERSE EFFECTS (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, adverse reaction rates 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.

Clinical trial data

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 the majority of 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).

Table 1 Adverse events reported in clinical trials

Metabolism and nutrition disorder	**rare:**	loss of/or poor appetite
	very rare:	dehydration
Nervous system disorders	**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

The following results were observed in a study of traveller's diarrhoea in tourists to Morocco where participants received either vaccine or killed *E. coli* K12 in sodium hydrogen carbonate buffer:

Table 2: Vaccine tolerability

Vaccine reaction	Placebo N=308 (%)	Vaccine N=307 (%)
Returned Vaccination forms	261/308 (84.7)	244/307 (79.5)
No symptoms	179 (68.6)	189 (77.5)
Abdominal discomfort	29 (11.1)	18 (7.4)
Loose stools	44 (16.9)	21 (8.6)
Headache	27 (10.3)	17 (7.0)
Rhinitis, cough or other respiratory symptoms	16 (6.1)	18 (7.4)
Other symptoms	8 (3.1)	11 (4.5)
%=n/Total reporting x 100 (returned Vaccination forms)		

In this study other symptoms among placebo recipients included: Oppressive feeling in diaphragm (N=1), bump below chin (N=1), itching red spots on back (N=1), intestinal gas (N=1), nausea (N=1), ache in shoulder (N=1), thirsty (N=1), nervousness (N=1). Other symptoms among vaccinees included: Nausea (N=4), fatigue (N=1), sore throat (N=1), intestinal gas (N=2), shivers (N=1), sense of fatigue (N=2).

Safety surveillance

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 suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Data on overdose are limited. Adverse reactions reported following overdose have been consistent with those seen after the recommended dosing, see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bacterial vaccines, ATC-code: J07AE01

The protection against cholera is specific for biotype and serotype. O-antigens as well as toxin B subunit will induce immunity. DUKORAL® contains additional antigenic components in order to induce broad protection. The vaccine contains no somatic or capsular antigens from O139 serogroup *Vibrio cholerae*, or from non-O1, non-O139 serogroup *Vibrio cholerae*.

Most enterotoxigenic *Escherichia coli* (ETEC) strains produce an enterotoxin, which is structurally, patho-physiologically and immunologically similar to cholera toxin. The heat labile enterotoxin, designated LT is neutralised by antibodies against cholera toxin subunit B.

Cholera infections are limited to the intestinal tract. Oral administration of DUKORAL® will induce local immunity.

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

Mechanism of action

DUKORAL® contains killed whole *V. 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 *E. coli* (ETEC) is structurally, functionally and immunologically similar to CTB. The two toxins cross-react immunologically.

Clinical trials

Clinical results have revealed a protective efficacy against cholera of 85% for the first six months in all age categories although efficacy had fallen to 52% at the end of the second year and 19% at the end of the third year. Children under the age of 2 were not examined, but protective efficacy in the 2-6-year age range was satisfactory (100%) for the first six months. In this randomised, double blind, placebo controlled study in Bangladesh, 3 doses of vaccine were given each separated by 6 weeks. Efficacy was measured 14 days after the 3rd dose. A cohort in this study received only two doses and the efficacy results were comparable with those who received three doses. The pivotal cholera efficacy studies were conducted in Bangladesh and Peru, where exposure to *Vibrio cholerae* prior to vaccination is likely to be greater than in Australia.

Table 3: Analysis of efficacy of DUKORAL® against cholera in children and adults in Bangladesh

	Children 2-6 years			**Adults and children > 6 years**		
Time after vaccination	Vaccine n=3,721 Cholera cases	Placebo n=3,800 Cholera cases	Protective Efficacy, % (95% CI)	Vaccine n=17,420 Cholera cases	Placebo n=17,420 Cholera cases	Protective Efficacy, % (95% CI)
6 months	0	9	100 (CI n.a.)	4	17	76 (30-92) p=0.009
Year 1	27	49	44 (10-65) p+0.016	20	82	76 (60-85) p<0.001
Year 2	17	26	33 (-23-64) n.s	23	58	60 (36-76) p<0.001
Year 3	23	18	<0	18	33	45 (3-69) p=0.038

Protective effectiveness of DUKORAL® 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 2 doses of DUKORAL® was 84% (95% CI 43-95, per-protocol analysis; p=0.005) for the initial 5 months of follow-up. Protective effectiveness of one or more doses of the vaccine was 78% (95% CI 39-92, intention-to-vaccinate analysis; p=0.004) (table 4).

An intention-to-vaccinate subgroup analysis was performed according to age selection and severity of cholera, where the effectiveness of the vaccine among those more than 15 years of age — an age group in which rates of HIV coinfection may be high— who have received one or more doses was 72 % (95% confidence interval, 24 to 91 %; p=0.03).

Table 4: Effectiveness of the oral cholera vaccine in Beira, Mozambique

Study and Analysis	**Vaccinees no./total no.(%)**		**Adjusted Odds Ratio (95% CI)**	**Vaccine Effectiveness (95% CI)**	**P Value**
Case-control study of VE	**Case Subjects**	**Controls**			
Intention-to-vaccinate analysis	10/43 (23)	94/172 (55)	0.22 (0.08 to 0.61)	78 (39 to 92)	0.004
Per-protocol analysis	8/39 (21)	80/156 (51)	0.16 (0.05 to 0.57)	84 (43 to 95)	0.005

In the longitudinal cohort-analysis conducted during the mass-vaccination campaign in Zanzibar, protective effectiveness after 2 doses of DUKORAL® was 79% (95% CI, 47-92; p<0.0001) for a follow-up period of 15 months. In addition to the direct protection, it was suggested that DUKORAL® provides indirect (herd) protection in the studied setting. (Table 5).

Table 5: Risk for cholera diarrhoea among vaccinated and non-vaccinated individuals by number of vaccine doses

Number of doses	Population	Cases of cholera diarrhoea	Incidence per 1000*	Relative risk (95% CI)	Vaccine effectiveness (p<0.0001)
0	20,500	33	1.61	1	-
1	3,757	3	0.80	0.54† (0.17 to 1.80)	46% (-80 to 83)
2	23,921	6	0.25	0.21† (0.08 to 0.53)	79% (47 to 92)

* incidence rate is calculated over the follow up period (Feb 27, 2009 to May 26, 2010)
† Adjusted for membership of geographical point of residence and significantly related variables with the risk of cholera

5.2 PHARMACOKINETIC PROPERTIES

Not applicable.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

DUKORAL® has not been evaluated for mutagenicity.

Carcinogenicity

DUKORAL® has not been evaluated for carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Vaccine, 1 dose (3mL) contains:	
Sodium phosphate, monobasic dihydrate	1.95mg
Sodium phosphate, dibasic dihydrate	9.39mg
Sodium chloride	25.5mg
Water for injections	to 3.0mL

Effervescent powder one sachet (5.6g) contains:	
Sodium bicarbonate	3600mg
Citric acid, anhydrous	1450mg
Raspberry flavour	70.0mg
Sodium carbonate anhydrous	400mg
Sodium citrate	6.0mg
Saccharin sodium	30.0mg

Refer to Section **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**.

6.2 INCOMPATIBILITIES

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.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2° to 8°C. REFRIGERATE. DO NOT FREEZE.

Do not use after expiry date.

After the powder has been dissolved in water and the vaccine suspension added, the mixture should be drunk within 2 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

DUKORAL® is available in the following pack sizes:

- Single Dose Carton: 1 vaccine vial and 1 sachet of effervescent powder
- Two Dose Carton: 2 vaccine vials and 2 sachets of effervescent powder

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

No data available

CAS number

Not applicable

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

Seqirus Pty Ltd ABN 26 160 735 035

63 Poplar Road

Parkville, VIC 3052

Australia

Telephone: 1800 642 865

Website: www.seqirus.com.au

9 DATE OF FIRST APPROVAL

Date of first inclusion in the Australian Register of Therapeutic Goods

09 September 2003

10 DATE OF REVISION

13 May 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2; 6.4	Drink prepared product within 2h
4.2	Correct age range for booster dose
4.5	Concomitant vaccination
5.1	Inclusion of Real World Data for two clinical trials
10	Date of revision updated