DUKORAL®
Oral inactivated cholera vaccine

Australian PI

NAME OF THE MEDICINE

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 cholera toxin B subunit.

DESCRIPTION

DUKORAL® is provided as a whitish oral liquid suspension (vaccine) in a single dose glass vial with white to off-white effervescent granules (buffer), in an accompanying sachet.

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

*bacterial count before inactivation

- Recombinant cholera toxin B subunit	1mg

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 granules, 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

PHARMACOLOGY

The protection against cholera is specific for both biotype and serotype. O-antigens as well as toxin B subunit will induce immunity. Many antigenic components have been included in the vaccine in order to give a good 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 will induce local immunity.

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

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 1: Bangladesh vaccine efficacy results against cholera

	Children < 6 years			Adults and children > 6 years		
Time after vaccination	Vaccine n=3,721 Cholera cases	Placebo n=3,800 Cholera cases	PE, % (95% CI)	Vaccine n=17,420 Cholera cases	Placebo n=17,420 Cholera cases	PE, % (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

INDICATIONS

Cholera caused by serogroup O1 *Vibrio cholerae*: 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.

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.

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 does not protect against *V. cholerae* serogroup O139 or other species of *Vibrio cholerae*.

In cholera, the efficacy of the vaccine is against clinical disease and the vaccine does not necessarily prevent spread of cholera via a vaccinee exposed to *V. cholerae* bacteria.

Cholera vaccine is not a sole measure in prevention of cholera outbreaks. Clean hygiene practices are still required.

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

The 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 subjects 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.

Use in Children
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 to be used in children less than 2 years of age.

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

Carcinogenicity, Mutagenicity, Effects on Fertility
DUKORAL® has not been evaluated for carcinogenicity, mutagenicity, or impairment of fertility.

Use in 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. 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.

Use in Lactation
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.

Effect on Ability to Drive and Use Machines
There is no evidence of an effect on the ability to drive and use machines.

Effect on Laboratory Tests
Not documented.

INTERACTIONS WITH OTHER MEDICINES
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 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 assessed in clinical studies. The administration of an encapsulated oral typhoid vaccine and DUKORAL® should be separated by at least 8 hours.

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

ADVERSE 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.

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

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

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).

Postmarketing 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

DOSAGE AND 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: In circumstances of ongoing risk or repeated travel, a 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.

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 granules.

Dissolve the effervescent granules 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 '**Interactions with other medicines**'.

DUKORAL® should only be mixed with the supplied effervescent granules 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.

OVERDOSAGE

Data on overdose are limited. Adverse reactions reported following overdose have been consistent with those seen after the recommended dosing, see '**Adverse effects'**.

For information on the management of overdose, contact the Poison Information

Centre on 131 126.

PRESENTATION AND STORAGE CONDITIONS

Presentation

DUKORAL® is provided as a whitish oral liquid suspension (vaccine) in a single dose glass vial with white to off-white effervescent granules (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 sizes:

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

Storage Conditions

Store at 2° to 8°C. REFRIGERATE. DO NOT FREEZE.
Do not use after expiry date.

NAME AND ADDRESS OF SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

Date of first inclusion in the ARTG:
09 September 2003

Date of most recent amendment:
06 August 2015

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