PRODUCT MONOGRAPH

DUKORAL®

Oral, Inactivated Cholera and ETEC Diarrhea Vaccine

Oral Suspension

Active Immunizing Agent for the Prevention of Diarrhea Caused
by *Vibrio cholerae* and/or heat-labile toxin producing Enterotoxigenic *Escherichia coli*

ATC Code: J07AE01

Manufactured by:
Valneva Sweden AB,
105 21 Stockholm,
Sweden

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Q&C Services
119-2550 Argentia Road
Mississauga, Ontario, L5N 5R1

Distributed by:
Valneva Canada Inc.
600-3535, Saint-Charles Blvd.
Kirkland, Québec, H9H 5B9

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DUKORAL®

Oral, Inactivated Cholera and ETEC DiarrheaVaccine

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration

Oral

Dosage Form/Strength

Oral Suspension

Vaccine	*V. cholerae* O1 Inaba classic strain, heat inactivated	ca. 31.25 x10^9 vibrios
	V. cholerae O1 Inaba El Tor strain, formalin inactivated	ca. 31.25 x 10^9 vibrios
	V. cholerae O1 Ogawa classic strain, heat inactivated	ca. 31.25 x 10^9 vibrios
	V. cholerae O1 Ogawa classic strain, formalin inactivated	ca. 31.25 x 10^9 vibrios
	Total	ca. 1.25 x 10^{11} vibrios

Recombinant cholera toxin B subunit (rCTB) 1 mg

Clinically Relevant Nonmedicinal Ingredients

Sodium Hydrogen Carbonate, one sachet (5.6 g) contains:
sodium hydrogen carbonate
saccharin sodium

For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING.

DESCRIPTION

DUKORAL® [Oral, Inactivated Cholera and ETEC Diarrhea Vaccine] 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. The vaccine is a whitish suspension in a single-dose glass vial. The sodium hydrogen carbonate is supplied as white effervescent granules with a raspberry flavour, to be dissolved in a glass of water before adding the vaccine. Each dose of vaccine is supplied with one sachet of sodium hydrogen carbonate.

INDICATIONS AND CLINICAL USE

DUKORAL® [Oral, Inactivated Cholera and ETEC Diarrhea Vaccine] is indicated for the prevention of and protection against cholera and ETEC- producing heat-labile enterotoxin (LT) (either LT alone or both LT and heat stable enterotoxin (ST) together).

Cholera: The vaccine is recommended for 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.

ETEC-diarrhea: The vaccine is recommended for adults and children from 2 years of age who will be visiting areas posing a risk of diarrheal illness caused by LT-producing ETEC.

DUKORAL® should be used in accordance with official recommendations taking into account the epidemiological variability and the risk of contracting diarrheal illness in different geographical areas and in different conditions of travel.

Onset of protection against cholera and LT-producing ETEC diarrhea can be expected about one week after the primary immunization series is completed. (1)

DUKORAL® should not replace standard preventive hygiene measures. Rehydration measures must be taken in case of diarrhea.

CONTRAINDICATIONS

Hypersensitivity to any component of DUKORAL® [Oral, Inactivated Cholera and ETEC DiarrheaVaccine] (see components listed in DOSAGE FORMS, COMPOSITION AND PACKAGING), or its container, to formaldehyde, or an anaphylactic or other hypersensitivity reaction to a previous dose of DUKORAL® is a contraindication to vaccination.

Immunization with DUKORAL® should be deferred in the presence of acute gastrointestinal illness or acute febrile illness to avoid superimposing adverse effects from the vaccine on the underlying illness or mistakenly identifying a manifestation of the underlying illness as a complication of vaccine use. A minor illness such as mild upper respiratory infection is not reason to defer immunization. (2)

WARNINGS AND PRECAUTIONS

General

DO NOT ADMINISTER THIS VACCINE PARENTERALLY. THIS VACCINE MUST BE TAKEN ORALLY (BY MOUTH) AFTER MIXING IT WITH THE BUFFER SOLUTION.

Before administration, take all appropriate precautions to prevent adverse reactions. This includes a review of the patient's history concerning possible hypersensitivity to the vaccine or similar vaccines, previous immunization history, the presence of any contraindications to immunization and current health status.

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

Before administration of the vaccine, health-care providers should inform the patient, parent or guardian of the benefits and risks of immunization, inquire about the recent health status of the patient and comply with any local requirements regarding information to be provided to the patient before immunization. Patients should be advised on the importance of taking the vaccine correctly (mixed with buffer and at dosing intervals of at least one week) and completing the immunization series at least one week before departure to achieve optimal protection.

Gastrointestinal

As with any vaccine, immunization with DUKORAL® [Oral, Inactivated Cholera and ETEC DiarrheaVaccine] may not protect 100% of susceptible persons. There are multiple aetiologies responsible for acute diarrhea in travelers. DUKORAL® can only confer protection against cholera and LT-producing ETEC. Therefore it should not replace standard preventive hygiene measures. Travellers should use care in the choice of food and water supply and use good hygienic measures. Rehydration measures must be taken in case of diarrhea.

Immune

Immunocompromised persons (whether from disease or treatment) may not obtain the expected immune response. (2) If possible, consideration should be given to delaying vaccination until after the completion of any immunosuppressive treatment.

DUKORAL® can be given to HIV-infected persons. Clinical trials have shown no vaccine-associated adverse events and no change in disease clinical progression. (3) (4) (5) Limited data are available on immunogenicity and safety of the vaccine. Vaccine protective efficacy has not been studied among HIV-infected persons. However, in a field study in Mozambique the protective efficacy was 84% in a population with approximately 25% HIV prevalence. (6)

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.

As with all products, the possibility of hypersensitivity reactions in persons sensitive to components of the vaccine should be evaluated.

DUKORAL® confers protection specific to *Vibrio cholerae* serogroup O1. DUKORAL® has not been demonstrated to protect against cholera caused by *V. cholerae* serogroup O139 or other species of Vibrio.

DUKORAL® confers protection specific to heat-labile enterotoxin (LT) producing ETEC (either LT alone or both LT and heat stable enterotoxin (ST). DUKORAL® has not been demonstrated to protect against ETEC strains that do not produce LT.

Neurologic

Potential Effect on Cognitive and Motor Performance

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

SPECIAL POPULATIONS

Pregnant Women

The effect of DUKORAL® [Oral, Inactivated Cholera and ETEC Diarrhea Vaccine] on embryo-fetal development has not been assessed and animal studies on reproductive toxicity have not been conducted. No specific clinical studies have been performed to address this issue. The vaccine is therefore not recommended for use in pregnancy. However, DUKORAL® is an inactivated vaccine that does not replicate. DUKORAL® is also given orally and acts locally in the intestine. Therefore, in theory, DUKORAL® should not pose any risk to the human fetus. Administration of DUKORAL® to pregnant women may be considered after careful evaluation of the benefits and risks.

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

Nursing Women

DUKORAL® may be given to breast-feeding women.

Pediatrics

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 children less than 2 years of age.

Geriatrics

DUKORAL® has been given to persons over the age of 65 in clinical trials, but there are only very limited data on protective efficacy of the vaccine in this age group. (7) However, this group can be expected to be at risk of more severe complications of disease if infected by cholera or LT-producing ETEC and therefore may obtain greater benefit from vaccination.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In clinical trials conducted in Bangladesh, Peru and Sweden, gastrointestinal symptoms were reported with similar frequency in vaccine and placebo groups. No serious adverse reactions were reported. (1) (8) (9)

Clinical Trial Adverse Drug Reactions

The safety of DUKORAL® [Oral, Inactivated Cholera and ETEC Diarrhea Vaccine] was assessed in clinical trials, including both adults and children from 2 years of age, conducted in endemic and non-endemic countries for cholera and LT-producing ETEC. 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 occurred at similar frequencies in vaccine and placebo groups. These included gastrointestinal symptoms including abdominal pain, diarrhea, loose stools, nausea and vomiting.

Frequency Classification

Very Common:	≥1/10 (≥10%)
Common (Frequent):	≥1/100 and <1/10 (≥1% and <10%)
Uncommon (Infrequent):	≥1/1,000 and <1/100 (≥0.1% and <1%)
Rare:	≥1/10,000 and <1/1,000 (≥0.01% and <0.1%)
Very Rare:	<1/10,000 (<0.01%), including isolated reports

Metabolism and Nutrition Disorders:

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	Diarrhea, 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-Market Adverse Drug Reactions

Additional adverse reactions reported during post-marketing surveillance are listed below:

Blood and lymphatic system disorders:

Lymphadenitis

Gastrointestinal disorders:

Flatulence

General disorders and administration site conditions:

Pain, flu-syndrome, asthenia, chills

Infections and infestations:

Gastroenteritis

Nervous system disorders:

Paraesthesia

Respiratory thoracic and mediastinal disorders:

Dyspnoea, increased sputum

Skin and subcutaneous tissue disorders:

Urticaria, angioedema, pruritus

Vascular disorders:

Hypertension

DRUG INTERACTIONS

Overview

There are obvious practical advantages to giving more than one vaccine at the same time, especially in preparation for foreign travel or when there is doubt that the patient will return for further doses of vaccine. Most of the commonly used antigens can safely be given simultaneously, except for those administered orally. No increase in the frequency or severity of clinically significant side effects has been observed. The immune response to each antigen is generally adequate and comparable to that found in patients receiving these vaccines at separate times.

Drug-Drug Interactions

The administration of an encapsulated oral typhoid vaccine and DUKORAL® [Oral, Inactivated Cholera and ETEC Diarrhea Vaccine] should be separated by at least 8 hours.

Oral administration of other vaccines and medicinal products should take place at least 1 hour before or at least 1 hour after DUKORAL® administration.

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. (7)

Drug-Food Interactions

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 must be avoided for 1 hour before and for 1 hour after vaccination.

To protect DUKORAL® from the acidic stomach environment, it has to be mixed with buffer solution (supplied effervescent buffer granules dissolved in water).

DOSAGE AND ADMINISTRATION

TO PREVENT CHOLERA:

Primary Immunization for adults and children 6 years and older:

- 2 oral doses at least 1 week apart.
- 1st dose at least 2 weeks before departure.
- 2nd dose at least 1 week after the 1st dose and at least 1 week before departure.
- Protection against cholera starts about 1 week after the second dose and will last for about 2 years.
- If more than 6 weeks elapse between the 1st and 2nd dose, the primary immunization should be re-started.

Booster for adults and children 6 years and older:

- If the patient received the last dose between 2 and 5 years before, one booster dose will be sufficient to renew the protection.
- If the patient received the last dose more than 5 years before, a complete primary immunization (2 doses) is recommended to renew the protection.

Primary Immunization for children 2 to 6 years:

- 3 oral doses at least 1 week apart and finishing at least 1 week before departure.
- 1st dose at least 3 weeks before departure; 2nd dose at least 1 week later; 3rd dose at least 1 week later and at least 1 week before departure.
- Protection against cholera starts about 1 week after the 3rd dose and will last for about 6 months for children 2 to 6 years.
- If more than 6 weeks elapse between any of the doses, the primary immunization should be re-started.

Booster for children 2 to 6 years:

- If the patient received the last dose between 6 months and 5 years before, one booster dose will be sufficient to renew the protection.
- If the patient received the last dose more than 5 years ago, a complete primary immunization (3 doses) is recommended to renew the protection.

TO PREVENT LT-producing ETEC DIARRHEA:

Primary Immunization for adults and children 2 years and older:

- 2 oral doses at least 1 week apart.

- 1st dose at least 2 weeks before departure.
- 2nd dose at least 1 week after the 1st dose and at least 1 week before departure.
- Protection against diarrhea caused by LT-producing ETEC starts about 1 week after the 2nd dose and will last for about 3 months.
- If more than 6 weeks elapse between the 1st and 2nd dose, the primary immunization should be re-started.

Booster for adults and children 2 years and older:

- If the patient received the last dose between 3 months and 5 years before, one booster dose will be sufficient to renew the protection.
- If the patient received the last dose more than 5 years before, a complete primary immunization (2 doses) is recommended to renew the protection.

Important Information about Taking DUKORAL®:

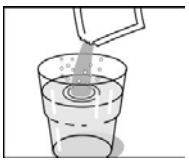
Do not eat or drink for 1 hour before and 1 hour after taking the vaccine.

Do not take any other medicine for 1 hour before and 1 hour after taking the vaccine.

Use only cool water to prepare the buffer solution to which the vaccine is added (see 'How to Prepare DUKORAL®.' below). **Do not use any other liquid.**

How to Prepare DUKORAL®:

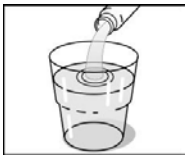
Prepare the buffer solution and add the vaccine according to the directions below:



1. Open the buffer sachet and dissolve the effervescent granules (sodium hydrogen carbonate) in 5 oz. (approx. 150 ml) of cool water.

   Children 2-6 years: pour away half of the solution.

2. Shake the vaccine vial (1 vial = 1 dose).



3. Add the vaccine to the sodium hydrogen carbonate solution. Mix well and drink the mixture. If the mixture is not drunk immediately it should be consumed within 2 hours of mixing. Keep it at room temperature.

Missed Dose

If the 2nd or 3rd dose is missed, it can be taken at any time within six weeks of the previous dose. Food and drink must be avoided for 1 hour before and 1 hour after.

Overdosage

Data on overdose are limited. Adverse reactions reported are consistent with those seen after the recommended dosing.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

DUKORAL® [Oral, Inactivated Cholera and ETEC Diarrhea Vaccine] consists of killed *V. cholerae* and the non-toxic recombinant cholera toxin B subunit. The vaccine acts locally in the gastrointestinal tract to induce an IgA antitoxic and antibacterial response (including memory) comparable to that induced by cholera disease itself. (10) The protection against cholera is specific for both Inaba and Ogawa serotypes and El Tor and Classical biotypes. O-antigens as well as toxin B subunit will induce immunity. (8) Most ETEC strains produce an enterotoxin called heat-labile enterotoxin (LT) which is structurally, pathophysiologically and immunologically similar to cholera toxin. This enterotoxin is neutralized by antibodies against cholera toxin B subunit. (9) (11) (12) Hence, the vaccine confers protection against cholera, as well as LT-producing ETEC, either LT alone or both LT and heat stable enterotoxin (ST) together.

Pharmacodynamics

In clinical trials DUKORAL® has been shown to prevent cholera caused by *V. cholerae* O1 (classical and El Tor biotypes) (13) (14) and diarrhea caused by enterotoxigenic *E. coli producing heat-labile enterotoxin* (LT-producing ETEC) (either LT alone or both LT and heat stable enterotoxin (ST) together) (9) (11). Protection against cholera and LT-producing ETEC diarrhea can be expected to start about one week after the primary immunization series is completed. (1)

DURATION OF EFFECT

Effect on 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, protective efficacy over a 3-year follow-up period averaged about 63% (without a booster dose). Children under the age of 2 were not examined, but protective efficacy in the 2-6 year age range was satisfactory for the first six months.

Effect on LT-producing ETEC diarrhea: Protective efficacy against LT-producing ETEC diarrhea lasts about 3 months. Protective efficacy with reference to all cause diarrhea will vary depending on the prevalence of LT-producing ETEC. There are considerable variations between different seasons and geographic areas.

STORAGE AND STABILITY

Store at 2° to 8°C (35° to 46°F). DO NOT FREEZE. The vaccine can be stored at room temperature (up to 25°C) for up to two weeks on one occasion only.

After mixing with the buffer solution the vaccine should be consumed within 2 hours.

The sodium hydrogen carbonate sachet may be stored separately at room temperature (up to 25°C).

Do not use after expiration date.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

The stopper of the vial for this product does not contain natural rubber latex.

DUKORAL® [Oral, Inactivated Cholera and ETEC Diarrhea Vaccine] is supplied in a package containing:

Package of 1 dose vial of vaccine and 1 sachet (5.6 g) sodium hydrogen carbonate.

Package of 2 x 1 dose vial of vaccine and 2 sachets (5.6 g) sodium hydrogen carbonate.

Package of 20 x 1 dose vial of vaccine and 20 sachets (5.6 g) sodium hydrogen carbonate.

Composition

Vaccine, one dose contains:

V. cholerae O1 Inaba classic strain, heat inactivated		ca. 31.25 x 10^9 vibrios
V. cholerae O1 Inaba El Tor strain, formalin inactivated		ca.31.25 x 10^9 vibrios
V. cholerae O1 Ogawa classic strain, heat inactivated		ca. 31.25 x 10^9 vibrios
V. cholerae O1 Ogawa classic strain, formalin inactivated		ca. 31.25 x 10^9 vibrios
	Total	ca. 1.25 x 10^{11} vibrios
Recombinant cholera toxin B subunit (rCTB)	1 mg	

Sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium chloride, water for injection to 3 mL.

Sodium Hydrogen Carbonate, one sachet (5.6 g) contains:
Sodium hydrogen carbonate, citric acid, sodium carbonate, saccharin sodium, sodium citrate, raspberry flavour.

One dose Dukoral® contains approximately 1.1 g sodium

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Oral, Inactivated Cholera and ETEC Diarrhea Vaccine

Each dose of vaccine is formulated to contain the following components:

Vaccine:

Component	Quantity (per dose)
V. cholerae O1 Inaba classic strain, heat inactivated	ca. 31.25 x 10^9 vibrios
V. cholerae O1 Inaba El Tor strain, formalin inactivated	ca. 31.25 x 10^9 vibrios
V. cholerae O1 Ogawa classic strain, heat inactivated	ca. 31.25 x 10^9 vibrios
V. cholerae O1 Ogawa classic strain, formalin inactivated	ca. 31.25 x 10^9 vibrios
Recombinant cholera toxin B subunit (rCTB)	1 mg
Sodium dihydrogen phosphate	
Disodium hydrogen phosphate	
Sodium chloride	
Water for injection	to 3 mL

Each sachet (5.6 g) of sodium hydrogen carbonate is formulated to contain the following components:

Sodium Hydrogen Carbonate:

Component	Quantity (per sachet)
Sodium hydrogen carbonate	3,600 mg
Citric acid	1,450 mg
Sodium carbonate	400 mg
Saccharin sodium	30.0 mg
Sodium citrate	6.0 mg
Raspberry flavour	70.0 mg

Product Characteristics

DUKORAL® [Oral, Inactivated Cholera and ETEC Diarrhea Vaccine] for oral use, is a whitish suspension consisting of four monovalent whole-cell bulks of *V. cholerae* O1 bacteria, either heat- or formalin-inactivated and one monovalent bulk of the recombinant non-toxic B-subunit of the cholera toxin (rCTB). The whole-cell bulks are grown in fermentors and the cells are thereafter harvested and concentrated. The concentrated suspension is then either subjected to heat inactivation or formalin inactivation. The formalin bulks are then subjected to a 2nd concentration step to remove residual formaldehyde. The gene for rCTB-213 is inserted in an expression vector in a *V. cholera* O1 strain. The expression of the rCTB is designed so that when the bacteria are grown the rCTB is overproduced and accumulates in the growth medium. The rCTB is isolated from the culture liquid by filtration and purified by precipitation and hydroxy apatite chromatography. The final vaccine is obtained by mixing the four monovalent cholera bulks with rCTB bulk and buffer.

CLINICAL TRIALS

Protective Efficacy

In clinical trials, DUKORAL® [Oral, Inactivated Cholera and ETEC Diarrhea Vaccine] has been shown to protect against cholera caused by *V. cholerae* O1 (classical and El Tor biotypes) (13) (14) and diarrhea caused by LT-producing enterotoxigenic *E. coli.* (9) (11)

Study Results - Efficacy

Cholera

In an efficacy study done in Bangladesh in 89,596 adults and children aged 2 years and older, the efficacy of DUKORAL® against cholera was 85% (12) (13) in the 6 months after the 3rd dose and 57% (14) in the second year after immunization. Protective efficacy declined over the 3-year study period, declining more rapidly in those under 6 years of age. (12) (13) (14)

An exploratory analysis suggested that 2 vaccine doses seemed as effective as 3 doses in adults.

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

Enterotoxigenic *E. coli*

In a randomized, 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 diarrhea caused by enterotoxigenic *E. coli* synthesizing heat-labile toxin (LT-producing ETEC) during the initial 3 months of follow-up but demonstrated no protection thereafter. (11) Protective efficacy against clinically severe episodes of LT-producing ETEC was 86%. Results are shown in Table 2.1.

Table 2.1: Vaccine Efficacy After 2 or 3 Doses (11)

	Efficacy % (p)	**CI 95% Lower Boundary**
ETEC LT Producers	67 (<0.01)	30
ETEC LT/ST*	73 (<0.01)	37
LT-ETEC Severe	86 (<0.05)	35

* ETEC LT/ST – ETEC synthesizing both heat-labile and heat-stable toxin.

In a prospective double-blind clinical trial done with 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. (9) Results are shown in Table 2.2

Table 2.2: Vaccine Efficacy After 2 Doses (9)

	Efficacy % (p)	**CI 95% (Range)**
ETEC LT producers	60 (0.04)	52:68
ETEC any	52 (0.01)	44:59
ETEC plus any other pathogen	71 (0.02)	N/A
ETEC plus *S. enterica*	82 (0.01)	76:88
All cause diarrhea*	23 (0.03)	16:30

*Protective efficacy with reference to all cause diarrhea will vary depending on the prevalence of LT producing ETEC. There are considerable variations between different seasons and geographic areas.

Immunogenicity

The vaccine-induced intestinal antitoxin IgA responses in 70-100% of vaccinated subjects. Serum vibriocidal and antitoxic antibodies have also been detected in vaccinated subjects. (10) A booster dose elicited an anamnestic response indicative of an immune memory. The duration of the adaptive immunological memory was estimated to last for at least 2 years in adults.

No established immunological correlates of protection against cholera after oral vaccination have been identified. There is a poor correlation between serum antibody responses, including vibriocidal antibody response and protection. Locally produced secretory IgA antibodies in the intestine probably mediate protective immunity.

Clinical Trial Adverse Reactions

In clinical trials conducted in Bangladesh, Peru and Sweden, gastrointestinal symptoms were reported with similar frequency in vaccine and placebo groups. No serious adverse reactions were reported. (1) (8) (9)

In a clinical trial conducted in Bangladesh, 321 persons received 3 doses of DUKORAL® [Oral, Inactivated Cholera and ETEC Diarrhea Vaccine] and 323 received a control buffer without vaccine. Adverse events reported following the first dose are shown in Table 2.3. The frequency of adverse events was similar following subsequent doses. There were no significant differences between the groups. No serious adverse reactions were reported.(15)

Table 2.3: Adverse Events Reported Following First Dose

Symptom	Treatment Group	
	BS/WC* (N = 321)	**Control (N = 323)**
Abdominal pain	52 (16%)	45 (14%)
Diarrhea	39 (12%)	34 (11%)
Subjective fever	13 (4%)	17 (5%)
Nausea	12 (4%)	16 (5%)
Vomiting	9 (3%)	4 (1%)
Hypersensitivity	0	0
Other†	1 (1%)	1 (1%)

* BS/WC – Cholera Toxin, B subunit with whole cell extract.

† Symptoms requiring bedrest. Complaints included headache and myalgias (1), generalized weakness and faintness (1), headache and coryza (1) and generalized weakness (1).

DETAILED PHARMACOLOGY

Cholera

Cholera is an acute intestinal infection caused by the bacterium *Vibrio cholerae*. It produces an enterotoxin that causes a copious, painless, watery diarrhea that can quickly lead to severe dehydration and death without proper treatment. Less than 10% of ill persons develop typical cholera with signs of moderate or severe dehydration. When illness does occur, more than 90% of episodes are mild or moderate severity and are difficult to distinguish clinically from other types of acute diarrhea. (23) Although oral rehydration may be life-saving, it has no effect on the course of the disease or dissemination of the infection. (24) In severe cases, antibiotic treatment is indicated, (23) however resistance is increasing. (25)

Infection is acquired primarily by ingesting contaminated water or food; person-to-person transmission is rare. (26) (24) Undercooked or raw shellfish and fish have been identified as sources of infection. (2) (27)

The World Health Organization (WHO) have recently concluded that cholera is re-emerging in parallel with populations who live in unsanitary conditions and many developing countries are facing an epidemic or risk of a cholera outbreak. (26) There was a sharp increase in the number of cholera cases reported to WHO during 2005, representing a 30% increase compared with the number of cases reported in 2004. Globally, the actual number of cholera cases is known to be much higher; the discrepancy is the result of under-reporting and other limitations of surveillance systems. (26) From 1995 - 2005, between 1 and 8 cases of cholera were reported annually in Canada. (28) Cholera has been recently reported in tourists. (29) (30)

Epidemiological reports suggest that the presence of cholera is more common in popular travel destinations than has previously been reported, *e.g.*, Thailand, China, Indonesia, India, Malaysia, South Africa, Brazil and Mexico. (7) Travellers who may be at significant increased risk for acquiring cholera include expatriates, such as relief and aid workers or health professionals working in endemic countries, as well as travellers returning to high-risk countries to visit friends and relatives. (31)

DUKORAL® consists of killed *V. cholerae* and the nontoxic recombinant cholera toxin B subunit. The vaccine acts locally in the gastrointestinal tract to induce an IgA antitoxic and antibacterial response (including memory) comparable to that induced by cholera disease itself. (10) The protection against cholera is specific for both biotype and serotype. O-antigens as well as toxin B subunit will induce immunity. (8)

LT-producing ETEC-diarrhea

Enterotoxigenic Escherichia coli (ETEC) is an important cause of diarrhea in infants and travelers to underdeveloped countries or regions of poor sanitation. Annually, ETEC is estimated to cause 200 million diarrheal episodes and approximately 380,000 deaths. (32) The disease requires colonization and elaboration of one or more enterotoxins. Episodes of ETEC diarrhea usually begin abruptly, either during travel or soon after returning home and are generally self-limited. In practice, the majority of diarrheal episodes resolve, even without treatment, after a period of between hours and weeks. While ETEC-associated diarrhea in adults has generally been thought of as a relatively mild, self limited disease, recent literature has highlighted a potential association with post-infection sequelae. Two separate meta-analyses have shown a 7-fold increase in the risk of developing post-infectious irritable bowel syndrome (PI-IBS), following an episode of acute infectious gastroenteritis (IGE), of which ETEC is a common cause and two studies have found this association in areas of high ETEC prevalence. (33)

Populations with increased susceptibility to ETEC diarrhea and higher risk for more severe disease caused by ETEC include persons with achlorhydia, gastrectomy, history of repeated severe diarrhea, young children > 2 years, immunosuppressed due to HIV infection with depressed CD4 count or other immunodeficiency states.

ETEC is transmitted by ingestion of food or water that is contaminated with enterotoxic strains of E. coli from human or animal feces. Strategies to prevent ETEC diarrhea in travelers include

education about the ingestion of safe food and beverages, vaccines, water purification, and chemoprophylaxis with non-antibiotic drugs or antibiotics.Although travellers are advised to take food, water and hygiene precautions to minimize their risk of enteric infection (19), the effectiveness of these measures is limited in practice.

Most ETEC strains produce an enterotoxin called heat-labile enterotoxin (LT) which is structurally, pathophysiologically and immunologically similar to cholera toxin. This enterotoxin is neutralized by antibodies against cholera toxin B subunit which is contained in Dukoral®. (9) (11) (12). Globally, 60% of ETEC isolates expressed LT either alone (27%) or in combination with ST (33%). (32)

The prevalence of LT only-expressing strains among travel populations was highest in Latin America/Carribean (38%). (32)

ETEC is the most common pathogen causing diarrhea during travel for many areas of the world (32). The epidemiology of specifically heat-labile toxin producing (either heat-labile toxin alone or both heat-labile and heat-stable toxins) ETEC strains has been documented to range from 5% to 20% (median 11%) of all isolates in studies on diarrhea in travellers and 1–27% (median 8%) in military studies. There are considerable variations between different seasons and geographic areas. Analysis of fifty-one published studies of diarrhea in travelers reported that Enterotoxigenic E. coli was detected in 30.4% (1,678/5,518) of all cases of diarrhea in travelers, with rates in Latin America/Caribbean of 33.6% (1,109/3,302), in Africa of 31,2% (389/1,217), in south Asia of 30,6% (153/499), and in Southeast Asia of 7.2% (36/500).

Mechanism of Action

DUKORAL® [Oral, Inactivated Cholera and ETEC Diarrhea Vaccine] 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. The vaccine is taken orally with bicarbonate buffer, which protects the antigens from gastric acid. ETEC infections and cholera are limited to the intestinal tract. It has been shown to be effective to administer the vaccine orally, which induces local immunity. 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 antitoxin intestinal antibodies prevent the cholera toxin from binding to the intestinal mucosal surface thereby preventing the toxin-mediated diarrheal symptoms.

After adherence to the intestinal mucosa, ETEC produce one or both of two enterotoxins, heat-labile enterotoxin (LT) and heat-stable enterotoxin (ST). LT has been shown to be immunogenic in humans (32). The heat-labile toxin (LT) of enterotoxigenic *E. coli* (ETEC) is structurally, functionally and immunologically similar to CTB. This enterotoxin is neutralized by antibodies against CTB. This means that DUKORAL® will also protect against diarrhea caused by LT producing ETEC.

Satisfactory protection against LT-producing ETEC diarrhea and cholera can be expected about one week after basic immunization is concluded.

TOXICOLOGY

Formal preclinical toxicology studies have not been performed because there are no relevant animal models for studying the effects of a LT-producing ETEC diarrhea or an oral cholera vaccine.

REFERENCE LIST

1 Jertborn M, *et al*. Evaluation of different immunization schedules for oral cholera B subunit whole-cell vaccine in Swedish volunteers. Vaccine 1993;11:1007-12.

2 National Advisory Committee on Immunization (NACI). General Guidelines. Vaccine Safety and Adverse Events Following Immunization. Recommended Immunization. Active Immunizing Agents - Cholera Vaccine. In: Canadian Immunization Guide. 7th ed. Her Majesty the Queen in Right of Canada, represented by the Minister of Public Works and Government Services Canada. 2006. p. 41,75,117-30,158.

3 Eriksson K, *et al*. Intestinal antibody responses to oral vaccination in HIV-infected individuals. AIDS 1993;7:1087-91.

4 Lewis DJM, *et al*. Immune response following oral administration of cholera toxin B subunit to HIV-1-infected UK and Kenyan subjects. AIDS 1994;8:779-85.

5 Ortigao-de-Sampaio MB, *et al*. Increase in plasma viral load after oral cholera immunization of HIV-infected subjects. AIDS 1998;12:F-145-50.

6 Lucas MES, *et al*. Effectiveness of mass oral vaccination in Beira, Mozambique. N Engl J Med 2005;352:757-67.

7 Data on file at Crucell Sweden AB (formerly SBL Vaccin AB).

8 Begue R, *et al*. Community-based assessment of safety and immunogenicity of the whole cell plus recombinant B subunit oral cholera vaccine in Peru. Vaccine 1995;13:691-4.

9 Peltola H, *et al*. Prevention of travellers' diarrhea by oral B-subunit/whole-cell cholera vaccine. Lancet 1991;338:1285.

10 Holmgren J, *et al*. New and improved vaccines against cholera: oral B subunit killed whole-cell cholera vaccines. In: New Generation Vaccines. Levine MM, *et al*. editors. New York: Marcel Dekker, Inc. 1997:459-68.

11 Clemens JD, *et al*. Cross-protection by B subunit whole-cell cholera vaccine against diarrhea associated with heat-labile toxin-producing enterotoxigenic Escherichia coli: results of a large scale field trial. J Inf Dis 1988;158:372-7.

12 Clemens JD, *et al*. Field trial of oral cholera vaccines in Bangladesh: results of one year of follow-up. J Inf Dis 1988;158:60-9.

13 Clemens JD, *et al*. Field trial of oral cholera vaccines in Bangladesh. Lancet 1986;2(8499):124-7.

14 Clemens JD, *et al*. Field trial of oral cholera vaccines in Bangladesh: results from three year follow-up. Lancet 1990;335:270-3.

15 Clemens JD, *et al*. B subunit whole-cell and whole-cell-only oral vaccines against cholera: studies on reactogenicity and immunogenicity. J Infect Dis 1987;155:79-85.

16 Centers for Disease Control and Prevention (CDC). Travellers' diarrhea. Health Information for International Travel 2008 (Yellow Book). Atlanta, GA: US Department of Health and Human Services. 2008 p. 322.

17 Ericsson CD, *et al*. editors. Travelers' Diarrhea. Hamilton, ON: BC Decker Inc.; 2003. p. 118, 126-8.

18 An Advisory Committee Statement (ACS) to Advise on Tropical Medicine and Travel (CATMAT) Statement on Travellers' Diarrhea. CCDR 2001;27 (ACS-3).

19 An Advisory Committee Statement (ACS) to Advise on Tropical Medicine and Travel (CATMAT) Statement on persistent diarrhea in the returned traveller. CCDR 2006;32(ACS-1):1-14.

20 Weinke T, *et al*. Immunisation prophylactique contre des souches d'Escherichia coli qui produisent de l'entérotoxine (ETEC) et contre le choléra qui peuvent être à l'origine des diarrhées des voyageurs: est-ce raisonnable et quelle est son importance et pour qui? Deutsche Medizinische Wochenschrift 2006;131:1-5.

21 Halvorson, *et al*. Postinfectious irritable bowel syndrome - a meta-analysis. Am J Gastroenterol 2006;101:8:1894-9.

22 Stermer E, *et al*. Is traveler's diarrhea a significant risk factor for the development of irritable bowel syndrome? A prospective study. Clin Infect Dis 2006;43:898-901.

23 World Health Organization (WHO). Cholera. Fact Sheet 107. Revised March 2000.

24 World Health Organization (WHO). Cholera vaccines: WHO position paper. Wkly Epidemiol Rec 2001;76:117-24.

25 ICDDR Centre for Health and Population Research. Emergence of a unique, multi-drug resistant strain of Vibrio cholerae O1 in Bangladesh. Health and Science Bulletin 2005;3:2:1-4.

26 World Health Organization (WHO). Cholera 2005. Wkly Epidemiol Rec 2006;81:297-308.

27 Parment PA. Cholera should be considered as a risk for travellers returning to industrialized countries. Trav Med and Infect Dis 2005;3:161-3.

28 Health Canada. Notifiable Disease On-Line. Cholera. Updated: 2006/01/20.

29 European Centre for Disease Prevention and Control (ECDC). Current cholera epidemics in West Africa and risks of imported cases in European countries. Eurosurveillance. 2005;10(9),050901.

30 European Centre for Disease Prevention and Control (ECDC). Cholera in Belgian tourists after travel to Turkey. Eurosurveillance. 2005;10(10),051013.

31 Steffen R, *et al*. Cholera: assessing the risk to travellers and identifying methods of protection. Trav Med and Infect Dis 2003;1:2:80-8.

32 Isidean S.D, *et al*. A systematic review of ETEC epidemiology focusing on colonization factor and toxin expression. Vaccine 2011; 29:6167-78.

33 Porter, C.K, et al. A systematic review of experimental infections with enterotoxigenic Escherichia coli (ETEC). Vaccine 2011; 29:5869-85.

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

DUKORAL®

Oral, Inactivated Cholera and ETEC Diarrhea Vaccine

This leaflet is part III of a three-part "Product Monograph" published when DUKORAL® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DUKORAL®. Contact your doctor or pharmacist if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is used for:

DUKORAL® is an oral vaccine that is used to help prevent diarrhea caused by enterotoxigenic *E. coli* (or ETEC) producing a heat sensitive toxin (called LT) and/or cholera. The ETEC bacterium is the most common cause of diarrhea in travellers. DUKORAL® is used to help protect people who are travelling to an area where there is a risk of diarrhea caused by cholera and/or LT-producing ETEC. This vaccine may be given to adults and children 2 years of age and older.

What the vaccine does:

DUKORAL® causes your body to produce its own protection against cholera and LT-producing ETEC diarrhea . After getting the vaccine, your body will make substances called antibodies, which fight the cholera and LT-producing ETEC bacteria and toxins that cause diarrhea. If a vaccinated person comes into contact with cholera or LT-producing ETEC bacteria the body is usually ready to destroy it.

It usually takes one week after you have completed all doses of the vaccine to be protected against diarrhea due to cholera or LT-producing ETEC. Most people who take the vaccine will produce enough antibodies to protect them against diarrhea caused by LT-producing ETEC or cholera. However, as with all vaccines, 100% protection is not guaranteed.

When it should not be used:

Do not use this vaccine in the following cases:

- Do not take DUKORAL® if you are allergic to any ingredient of the vaccine or to formaldehyde.
- Do not give DUKORAL® to a child who is allergic to any ingredient of the vaccine or to formaldehyde.
- Do not give DUKORAL® to a person who has a fever or acute gastrointestinal illness (e.g. diarrhea). Wait until the person is better to give the vaccine. Consult your doctor, nurse or pharmacist for guidance.

Talk to your doctor, nurse or pharmacist if you are not sure whether you or your child should take DUKORAL®.

What the medicinal ingredient is:

Each single-dose vaccine vial contains:
V. cholera O1 Inaba classic strain, heat inactivated
V. cholera O1 Inaba El Tor strain, formalin inactivated
V. cholerae O1 Ogawa classic strain, heat inactivated
V. cholerae O1 Ogawa classic strain, formalin inactivated
Recombinant cholera toxin B subunit (rCTB)

What the important nonmedicinal ingredients are:

Each Sodium Hydrogen Carbonate sachet contains:
Sodium hydrogen carbonate, saccharin sodium.

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

One dose Dukoral contains approximately 1.1 g sodium.

What dosage forms it comes in:

DUKORAL® is a liquid vaccine that must be swallowed (taken orally) after adding it to a buffer solution. DUKORAL® comes in a carton containing one or two doses.

The vaccine is a small amount of whitish suspension in a single-dose glass vial.

Each dose of vaccine comes with one sachet package that contains white granules of sodium hydrogen carbonate. The granules are to be dissolved in a glass of water – do not use any other liquid. The vaccine is then added and mixed with this buffer solution. The vaccine mixture has a raspberry taste.

WARNINGS AND PRECAUTIONS

If you have any of the following conditions, talk to your doctor, nurse or pharmacist BEFORE you take DUKORAL®:

- **Persons who have diseases of the immune system or who take a medical treatment that affects the immune system.** The vaccine may provide you with a lower level of protection than it does for people with healthy immune systems.
- **Persons who have an allergy to any component of the vaccine or the container or to formaldehyde.**
- **Persons who have acute gastrointestinal illness (e.g. diarrhea) or high temperature.** You may need to postpone taking DUKORAL® until the illness has passed. You may take the vaccine if you have a mild illness, such as a cold.
- **Pregnant women.** DUKORAL® is not recommended for use in pregnancy. Your doctor will discuss the possible risks and benefits of having DUKORAL® during pregnancy.

DUKORAL® prevents diarrhea caused by cholera and LT-producing ETEC. It will not prevent diarrhea caused by other organisms. While travelling, be careful when choosing food and wash, peel or cook it yourself if possible. Drink bottled or boiled water. If possible, wash hands before eating and after using toilet facilities.

As with any vaccine, immunization with DUKORAL® may not protect 100% of susceptible persons.

INTERACTIONS WITH THIS VACCINE

Do not eat, drink or take other medicine for 1 hour before and for 1 hour after taking the vaccine. Food and drink taken during this time may prevent the vaccine from working.

PROPER USE OF THIS VACCINE

TO PROTECT AGAINST CHOLERA:

Primary vaccination course for adults and children 6 years and older: Take 2 doses orally (by mouth) at least 1 week (up to 6 weeks) apart. Take the 2nd dose at least 1 week after the first dose and at least 1 week before your trip. It takes about 1 week after the last dose for protection to begin. Protection against cholera lasts for about 2 years. If you wait more than 6 weeks between the 1st and 2nd dose, you will have to start again with the 1st dose.

Booster for adults and children over 6 years: If you had your last dose of the vaccine between 2 and 5 years before, a single dose will renew your protection. If more than 5 years has passed since your last dose, you should have the complete primary vaccination course (2 doses) again.

Primary vaccination course for children 2 to 6 years: Give 3 doses orally (by mouth) at least 1 week (up to 6 weeks) apart and finishing at least 1 week before the trip.

Give the 1st dose at least 3 weeks before the trip, the 2nd dose at least 1 week after the 1st dose, and the 3rd dose at least 1 week after the 2nd dose. It takes about 1 week after the last dose for protection to begin. Protection against cholera will last for about 6 months. If more than 6 weeks elapse between any of the doses, the child will have to start again with the 1st dose.

Booster for children 2 to 6 years: If the child had the last dose of the vaccine between 6 months and 5 years before, a single dose will renew protection. If more than 5 years has passed since the last dose, complete primary vaccination course (3 doses) is recommended

TO PROTECT AGAINST DIARRHEA CAUSED BY LT-producing ETEC:

Primary vaccination course for adults and children 2 years and older: 2 doses orally (by mouth) at least 1 week (up to 6 weeks) apart. Take the 1st dose no later than 2 weeks before you leave for your trip. Take the 2nd dose at least 1 week after the 1st dose and at least 1 week before your trip. It takes about 1 week after the last dose for protection to begin.

Protection against diarrhea caused by LT-producing ETEC starts about 1 week after the 2nd dose and lasts for about 3 months. If you wait more than 6 weeks between the 1st and 2nd dose, you will have to start again with the 1st dose.

Booster: If you had your last dose of the vaccine between 3 months and 5 years before, a single dose will renew your protection. If more than 5 years has passed since your last dose, you should have the complete primary vaccination course (2 doses) again.

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Important Information about Taking DUKORAL®:

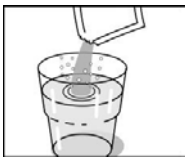
The vaccine has to be taken mixed with a buffer solution to protect it from the stomach acid. Use only cool water to prepare the buffer solution. Do not use any other liquid.

Do not eat or drink for 1 hour before and for 1 hour after taking the vaccine.

Do not take any other medicine orally (by mouth) for 1 hour before and 1 hour after taking the vaccine.

Follow the directions for proper mixing as shown below. It is important to follow these instructions to make sure the vaccine works.

How to take DUKORAL®:



Step 1: **Prepare the buffer solution:**

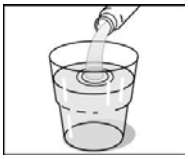
Open the buffer sachet and dissolve the granules in 5 oz (150 mL) of cool water. **Do not use any other liquid.**

For adults and children 6 years and older - proceed to Step 2.

For children 2 to 6 years - pour away half of the solution before proceeding to Step 2.

Step 2: Shake the vaccine vial

Shake the small glass vial that contains the vaccine to mix it well.



Step 3: **Mix the vaccine with the buffer solution**

Open one vial and add the vaccine to the buffer solution (water and granule mixture) in the glass. Stir well and drink this mixture immediately.

If the mixture is not drunk immediately, it should be consumed within 2 hours of mixing. Keep it at room temperature.

Your doctor or pharmacist will tell you how to take this vaccine. **Follow their directions carefully. If you do not understand the instructions, ask your doctor, nurse or pharmacist for help.**

When to take DUKORAL®:

It is important to take DUKORAL® at the right time to make sure you will be protected against cholera and LT-producing ETEC diarrhea .

Make sure that you take each of the doses at least 1 week (up to 6 weeks) apart.

Make sure that you take the last dose of vaccine at least 1 week before leaving on your trip.

Missed Dose

You can take the 2nd dose of DUKORAL® up to 6 weeks after the 1st dose (children 2 to 6 years have to take 3 doses to protect against cholera).

If the 2nd (or 3rd) dose is missed, it can be taken at any time within 6 weeks of the previous dose. Food and drink must be avoided for 1 hour before and for 1 hour after taking the vaccine.

Overdose

If you take more than the recommended dose, you may have some of the side effects listed below.

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

If you are not sure what to do ask your doctor, nurse or pharmacist.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

A vaccine, like any medicine, may cause serious problems, such as severe allergic reactions. The risk of DUKORAL® causing serious harm is extremely small. The small risks associated with DUKORAL® are much less than the risks associated with getting the diseases.

Tell your doctor, nurse or pharmacist as soon as possible if you do not feel well after receiving DUKORAL®.

The side effects of DUKORAL® are usually mild. The most common side effects are gastrointestinal upsets, such as abdominal pain, diarrhea, nausea or vomiting. Some people who receive DUKORAL® may feel feverish. Potentially serious side effects (e.g., dehydration, shortness of breath) are extremely rare.

This is not a complete list of side effects. For any unexpected effects while taking DUKORAL®, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

Store the vaccine in a refrigerator at 2° to 8°C (35° to 46°F). DO NOT FREEZE DUKORAL®. Freezing destroys the vaccine.

The vaccine can be stored at room temperature (up to 25°C) for up to two weeks on one occasion only.

After mixing with the buffer solution, the vaccine should be taken within 2 hours.

Do not use after expiration date**. Do not take DUKORAL® after the expiry date printed on the carton.**

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

For health care professionals:
If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in **your province/territory**.

For the General Public:
Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.
If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada
By toll-free telephone: 866-844-0018
By toll-free fax: 866-844-5931
Email: caefi@phac-aspc.gc.ca
Web: http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php
Mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road, A/L 6502A
Ottawa, ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health-care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

MORE INFORMATION

The full product monograph, prepared for health professionals can be found at www.valneva.ca or by contacting Medical Information at Valneva Canada Inc. at 1-855-356-0831. Business hours: 9:00 a.m. to 5:00 p.m. Eastern Time, Monday to Friday.

This leaflet was prepared by Valneva Sweden AB.

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