Cholera is an important public health problem worldwide and is endemic in 69 countries[8,9,10]

According to the World Health Organization:[9]

- Researchers have estimated 1.3 to 4 million cholera cases occur annually, and 21,000 to 143,000 deaths worldwide.
- During 2020, 323,369 cases and 857 deaths were notified from 24 countries.
- The discrepancy between these figures and the estimated burden of the disease is due to under-reporting, limitations in surveillance systems, and fear of impact on trade and tourism.

Active cholera transmission occurs in a number of regions[11]



Adapted from the CDC (2022)

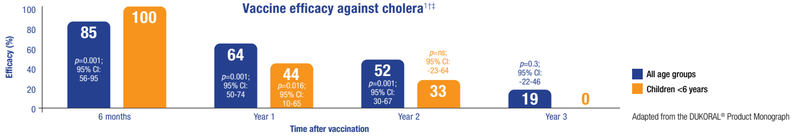
- Cholera is an acute intestinal infection caused by the bacterium *Vibrio cholera*, which can lead to copious, painless, and watery diarrhea, and if not treated properly, severe dehydration and death.[12]
- Infection is acquired primarily by ingesting contaminated water or food; person-to-person transmission is rare.[12]
- Practice safe food and water precautions.[3]
- Wash your hands frequently.[3]
- Consider getting vaccinated. High-risk travellers, such as those visiting areas with limited access to clean food, water and proper sanitation, may benefit from vaccination.[9,13,14]

DUKORAL® is used to prevent cholera in travellers.[1]
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.
DUKORAL® is not indicated to reduce dehydration or prevent death.

DUKORAL® demonstrated protective efficacy against cholera[1]

Clinical trials were conducted with an earlier composition of DUKORAL®, formulated with purified native cholera toxin B subunit (CTB; referred to as BS in the clinical trials) and killed cholera whole cell extract (WC). The current composition of DUKORAL® contains recombinant cholera toxin B (rCTB), shown to be immunologically equivalent to native CTB. Two studies conducted in a total of 107 Swedish volunteers demonstrated comparable antitoxin and vibriocidal antibody titers after immunization with either rCTB or native CTB.

Vaccine efficacy against cholera[1†‡]



Adapted from the DUKORAL® Product Monograph

Number of cholera cases at 6 months, 1 year, 2 years, and 3 years were: (WC/BS vaccinated group, all ages) 4, 47, 40, and 41, respectively; (placebo group, all ages) 26, 131, 84, and 51, respectively; (WC/BS vaccinated group, children <6) 0, 27, 17, and 23, respectively; (placebo group, children <6) 9, 49, 26, and 18, respectively.

Protective efficacy declined over the 3-year study period, declining more rapidly in those under 6 years of age.[1]

Proven safety profile[1]

- In clinical trials in adults and children above 2 years, 321 persons received three doses of DUKORAL® formulated with purified native cholera toxin B subunit (BS) and killed cholera whole cell extract (WC); and 323 persons received a control buffer without vaccine. The most frequently reported adverse events were gastrointestinal symptoms including abdominal pain (16% with DUKORAL®, 14% with placebo), diarrhea (12%, 11%), nausea (4%, 5%), and vomiting (3%, 1%), general disorders and administration site conditions including subjective fever (4%, 5%) and other symptoms requiring bedrest. Complaints included headache and myalgias (1), generalized weakness and faintness (1), headache and coryza (1) and generalized weakness (1) (1%, 1%) in DUKORAL® and placebo groups, respectively. There were no significant differences between the groups.§

ns: not statistically significant
† A randomized, double-blind field study done in Bangladesh investigating vaccine efficacy against cholera during the 3 year study period. 89,152 adults and children aged 2 years and older received at least one dose of study medication, of whom 63,498 received three complete doses given at 6 week intervals. Subjects in each treatment group received either killed cholera whole cells (WC), with or without the purified native form of the cholera toxin B-subunit (BS) (n=21,141 and n=21,137, respectively), or placebo (n=21,220). Number of children <6 years in each treatment group were (WC/BS) 3,721, (WC) 3,871, and (placebo) 3,800.[1]
‡ An exploratory analysis suggested that 2 vaccine doses seemed as effective as 3 doses in adults.[1]
§ Clinical trials assessed the safety of DUKORAL® in both adults and children from 2 years of age in endemic and non-endemic countries for cholera and ETEC-producing heat-labile enterotoxin (LT). More than 94,000 doses of DUKORAL® were administered during the clinical trials. In the majority of studies, adverse events were assessed by passive surveillance. The evaluation of safety varied between trials with respect to mode of surveillance, definition of symptoms and time of follow-up.

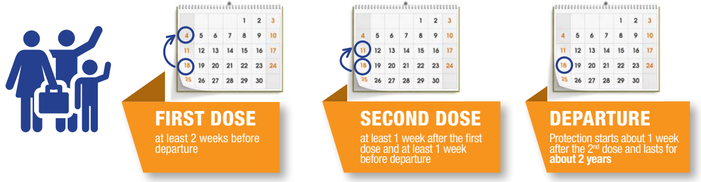
When patients should take DUKORAL®

To prevent cholera[1]

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.

Adult or child 6 years or older taking DUKORAL® for the first time

(primary immunization, 2 doses)



NOTE: If more than 6 weeks elapse between the 1st and 2nd dose, the primary immunization should be re-started.

Child between 2 and 6 years old taking DUKORAL® for the first time

(primary immunization, 3 doses)



NOTE: If more than 6 weeks elapse between any of the doses, the primary immunization should be re-started.

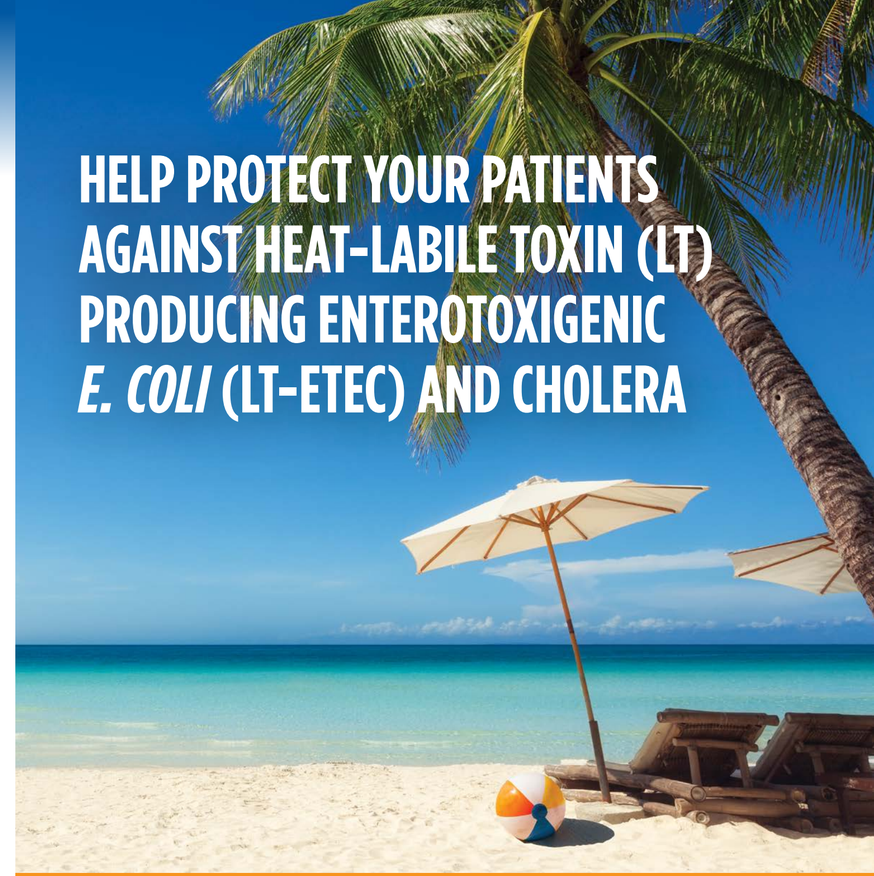
Booster

Adult or child 6 years or older who has taken DUKORAL® before and is travelling again

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

Child between 2 and 6 years old who has taken DUKORAL® before and is travelling again

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



HELP PROTECT YOUR PATIENTS AGAINST HEAT-LABILE TOXIN (LT) PRODUCING ENTEROTOXIGENIC *E. COLI* (LT-ETEC) AND CHOLERA

DUKORAL® [Oral, Inactivated Cholera and LT-producing ETEC Diarrhea Vaccine] is indicated for the prevention of and protection against cholera and diarrhea caused by heat-labile toxin producing enterotoxigenic *Escherichia coli* (LT-ETEC) in adults and children from 2 years of age.

DUKORAL®

Facts about LT-ETEC

- Enterotoxigenic *E. coli* (ETEC) is the most common pathogen causing diarrhea during travel for many areas of the world.[2]
- Globally, 60% of ETEC isolates produce a heat-labile toxin (LT), either LT alone (27%) or the combination of LT and heat-stable toxin (33%).[6]

One of the most important risk factors is the geographical travel destination[4]

Average incidence of LT-ETEC by region[5,6]





Adapted from Shah *et al.* 2009 and Isidean *et al.* 2011

DUKORAL® is used to prevent LT-producing enterotoxigenic *E. coli* (ETEC) diarrhea in travellers.[1]

* **LT-producing ETEC:** ETEC strains expressing LT alone or both LT and ST enterotoxins together (proportion among collected ETEC isolates)

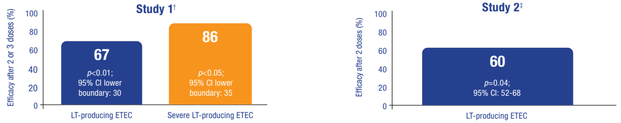
- LT-ETEC is transmitted by eating food or drinking water that is contaminated with enterotoxic strains of *E. coli* from human or animal feces.[3]
- Infection with LT-ETEC can cause profuse watery diarrhea.[7]
- Although ETEC infection is usually self-limiting, lasting 3 to 4 days, some episodes, particularly due to LT-ETEC go on to become persistent diarrhea lasting longer than 14 days.[15]

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.[1]

DUKORAL® demonstrated protective efficacy against LT-producing ETEC diarrhea[1]

Clinical trials were conducted with an earlier composition of DUKORAL®, formulated with purified native cholera toxin B subunit (CTB; referred to as BS in the clinical trials) and killed cholera whole cell extract (WC). The current composition of DUKORAL® contains recombinant cholera toxin B (rCTB), shown to be immunologically equivalent to native CTB. Two studies conducted in a total of 107 Swedish volunteers demonstrated comparable antitoxin and vibriocidal antibody titers after immunization with either rCTB or native CTB.

Vaccine efficacy against episodes of diarrhea caused by LT-producing ETEC



Adapted from the DUKORAL® Product Monograph

DUKORAL® had an **86% protective efficacy** against clinically severe episodes of LT-producing ETEC

Help prevent LT-producing enterotoxigenic *E. coli* diarrhea with DUKORAL®

† A randomized, double-blind field study done in Bangladesh investigating vaccine efficacy after 2 or 3 doses against episodes of diarrhea caused by LT-producing ETEC during the initial 3 months of follow-up. 89,152 adults and children aged 2 years and older received at least one dose of study medication, of whom 63,498 received three complete doses given at 6 week intervals.[1]

‡ A prospective double-blind trial investigating vaccine efficacy after 2 doses against episodes of diarrhea caused by different types of ETEC in 615 healthy Finnish tourists travelling to Morocco aged 15 years and older. Each patient received 2 doses of either DUKORAL® (n=307) or placebo (n=308) before the trip departure.[1]

When patients should take DUKORAL®

To prevent diarrhea caused by LT-producing enterotoxigenic *E. coli*[1]

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.

Patients taking DUKORAL® for the first time (primary immunization, 2 doses)[1]

Adults and children 2 years and older



FIRST DOSE
at least 2 weeks before departure



SECOND DOSE
at least 1 week after the first dose and at least 1 week before departure



DEPARTURE
Protection starts about 1 week after the 2nd dose and lasts for about **3 months**

NOTE: If more than 6 weeks elapse between the 1st and 2nd dose, the primary immunization (2 doses) should be re-started.

Booster

If your patient has taken DUKORAL® before and is travelling again

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

How to prepare DUKORAL®

Locate the two components: effervescent powder (sodium hydrogen carbonate) in a white sachet and the DUKORAL® vaccine vial.
Prepare the buffer solution (effervescent powder+water mixture) and add the content of the DUKORAL® vaccine vial according to the directions below:



Step 1
To prepare the buffer solution: Open the white sachet of effervescent powder (sodium hydrogen carbonate) and pour its content into 150 mL (approx. 5 oz) of cool water. Stir gently with a spoon to dissolve. Use only cool water to prepare the buffer solution. Do not use any other liquid.
For kids aged 2–6 years, pour away half of the water/powder mixture before proceeding to Step 2 (keep 75 mL, approx. 2.5 oz).



Step 2
Shake the DUKORAL® vaccine vial
(1 vial = 1 dose).



Step 3
To prepare the vaccine mixture: Open the DUKORAL® vaccine vial (see Step 2) and pour its content into the glass of prepared buffer solution (see Step 1). Stir gently with a spoon to mix all ingredients.



Step 4
Drink the entire vaccine mixture (see Step 3) immediately, as it should be consumed within 2 hours after its preparation. Keep the mixture at room temperature if not drunk immediately.

IMPORTANT: Do not eat or drink any other liquids (including water), or take any other medication for 1 hour before and 1 hour after taking the vaccine mixture.

Convenient oral vaccine

STORAGE:

STORE IN THE REFRIGERATOR
at 2° to 8°C (35° to 46°F).
DO NOT FREEZE.

Do not use after expiry date.
After mixing the content of the DUKORAL® vaccine vial with the buffer solution (effervescent powder+water mixture), the vaccine mixture should be consumed within 2 hours.

Keep out of reach and sight of children.



Contraindications:

- Hypersensitivity to any component of DUKORAL® or its container, to formaldehyde, or an anaphylactic or other hypersensitivity reaction to a previous dose of DUKORAL®.
- Immunization with DUKORAL® should be deferred in the presence of acute gastrointestinal illness or acute febrile illness.

Most serious warnings and precautions:

- **Administration:** DO NOT ADMINISTER THIS VACCINE PARENTERALLY. THIS VACCINE MUST BE TAKEN ORALLY (BY MOUTH) AFTER MIXING IT WITH THE BUFFER SOLUTION.
- **Gastrointestinal:** As with any vaccine, immunization with DUKORAL® may not protect 100% of susceptible persons. There are multiple etiologies responsible for acute diarrhea in travellers. 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. 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. Limited data are available on immunogenicity and safety of the vaccine. Vaccine protective efficacy has not been studied among HIV-infected persons.
- 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 LT-producing ETEC (either LT alone or both LT and heat-stable enterotoxin (ST) together). DUKORAL® has not been demonstrated to protect against ETEC strains that do not produce LT.

Other relevant warnings and precautions:

- 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 1.2 g sodium per dose, which should be taken into consideration by patients on a controlled sodium diet.
- Before administration of the vaccine, healthcare 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.
- 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.
- There are only very limited data on protective efficacy of the vaccine in the geriatric population. However, this population 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.
- Populations with increased susceptibility to cholera and LT-producing ETEC diarrhea and who are at higher risk for more severe disease 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.

For more information:

Please consult the DUKORAL® Product Monograph at https://health-products.canada.ca/dpd-bdpp/index-eng.jsp for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece.

The Product Monograph is also available by calling 1-855-356-0831.

The drug identification number (DIN) for DUKORAL® is 02247208.

References: 1. DUKORAL® Product Monograph. July 27, 2022. **2.** Center of Disease Control. Traveler's Diarrhea. November 22, 2019. **3.** Center of Disease Control. Enterotoxigenic *E. coli* (ETEC). December 1, 2014. **4.** Steffen R. Epidemiology of travellers' diarrhea. *J Travel Med.* 2017;24(suppl_1):S2–S5. **5.** Shah N, *et al.* Global etiology of traveler's diarrhea: Systematic Review from 1973 to the present. *Am J Trop Med Hyg* 2009; 80(4):609–614. **6.** Isidean SD, *et al.* A systematic review of ETEC epidemiology focusing on colonization factor and toxin expression. *Vaccine* 2011; 29:6167–78. **7.** World Health Organization. WHO preferred product characteristics for vaccines against enterotoxigenic Escherichia coli. May 31, 2021. Available online: https://www.who.int/publications/i/item/who-preferred-product-characteristics-for-vaccines-against-enterotoxigenic-escherichia-coli. **8.** Mohammad A, *et al.* The global burden of cholera. *Bulletin of the World Health Organization* 2012; 90(3):209–218A. **9.** World Health Organization. Cholera Fact sheet. March 2022. **10.** Hsiao A, *et al.* Lessons learnt from 12 oral cholera vaccine campaigns in resource-poor settings. *Bulletin of the World Health Organization* 2017;95:303–312. **11.** Centers for Disease Control and Prevention. Cholera. Available online: https://wwwnc.cdc.gov/travel/diseases/cholera (Accessed February 2022). **12.** Pan American Health Organization. Cholera. Available online: https://www.paho.org/en/topics/cholera. **13.** Canadian Immunization Guide. Cholera and enterotoxigenic escherichia coli (ETEC) travellers' diarrhea vaccine. April 2017. **14.** Travel.gc.ca. Cholera in West Africa. March 03, 2021. **15.** Khalil I, Walker R, Porter C, *et al.* Enterotoxigenic Escherichia coli (ETEC) vaccines: Priority activities to enable product development, licensure, and global access. *Vaccine* 2021;Jul 13;39(31):4266–4277. **16.** Henrique C, *et al.* Heat-Labile Toxin from Enterotoxigenic Escherichia coli Causes Systemic Impairment in Zebrafish Model. *Toxins* 2021;13:419.

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