PRODUCT MONOGRAPH

DUKORAL®

Oral, Inactivated Travellers' Diarrhea and Cholera Vaccine

Oral Suspension

Active Immunizing Agent for the Prevention of Travellers' Diarrhea Caused by Enterotoxigenic *Escherichia coli* and/or Cholera caused by *Vibrio cholerae*

ATCC Code: J07AE01

Sanofi Pasteur Limited
Toronto, Ontario, Canada

Date of Approval:
November 2007

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DUKORAL®

Oral, Inactivated Travellers' Diarrhea and Cholera Vaccine

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. 2.5 x 10^{10} vibrios
	V. cholerae O1 Inaba El Tor strain, formalin inactivated	ca. 2.5 x 10^{10} vibrios
	V. cholerae O1 Ogawa classic strain, heat inactivated	ca. 2.5 x 10^{10} vibrios
	V. cholerae O1 Ogawa classic strain, formalin inactivated	ca. 2.5 x 10^{10} vibrios
	Total	ca. 1 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 section.

DESCRIPTION

DUKORAL® [Oral, Inactivated Travellers' Diarrhea and Cholera 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, which should be dissolved in a glass of water. Each dose of vaccine is supplied with one sachet of sodium hydrogen carbonate.

INDICATIONS AND CLINICAL USE

DUKORAL® [Oral, Inactivated Travellers' Diarrhea and Cholera Vaccine] is indicated for the prevention of and protection against travellers' diarrhea (TD) and/or cholera in adults and children 2 years of age and older who will be visiting areas where there is a risk of contracting TD caused by enterotoxigenic *Escherichia coli* (ETEC) or cholera caused by *V. cholerae.*

Protection against ETEC diarrhea and cholera can be expected about one week after the primary immunization series is completed. (1)

CONTRAINDICATIONS

Allergy to any component of DUKORAL® [Oral, Inactivated Travellers' Diarrhea and Cholera Vaccine] (see components listed in DOSAGE FORMS, COMPOSITION AND PACKAGING), or its container, or an anaphylactic or other allergic reaction to a previous dose of DUKORAL® is a contraindication to vaccination.

Immunization with DUKORAL® should be deferred in the presence of any acute illness, including 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).

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 vaccine, previous immunization history, the presence of any contraindications to immunization and current health status.

Before administration of any 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 and the importance of completing the immunization series.

Gastrointestinal

As with any vaccine, immunization with DUKORAL® [Oral, Inactivated Travellers' Diarrhea and Cholera Vaccine] may not protect 100% of susceptible persons.

Travellers should use care in the choice of food and water supply and use good hygienic measures.

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 allergic 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.

SPECIAL POPULATIONS

Pregnant Women

The effect of DUKORAL® [Oral, Inactivated Travellers' Diarrhea and Cholera 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.

Nursing Women

DUKORAL® may be given to lactating 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 ETEC or cholera 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 Travellers' Diarrhea and Cholera Vaccine] was assessed in clinical trials, including both adults and children, conducted in endemic and non-endemic countries for cholera and 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 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 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	Diarrhea, abdominal pain, abdominal cramps, stomach/abdominal gurgling (gas), abdominal discomfort
Rare	Nausea, vomiting
Very Rare	Dyspepsia, sore throat

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 (very rare <1/10,000) during post-marketing surveillance, following distribution of approximately 7,000,000 vaccine doses, 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

Physicians, nurses and pharmacists should report any adverse occurrences temporally related to the administration of the product in accordance with local requirements and to the Global Pharmacovigilance Department, Sanofi Pasteur Limited, 1755 Steeles Avenue West, Toronto, ON, M2R 3T4, Canada. 1-888-621-1146 (phone) or 416-667-2435 (fax).

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. 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 Travellers' Diarrhea and Cholera Vaccine] should be separated by at least 8 hours.

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

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

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

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

DOSAGE AND ADMINISTRATION

TO PREVENT TRAVELLERS' DIARRHEA CAUSED BY ETEC:

Primary Immunization for adults and children 2 years and older:

- 2 doses orally at least 1 week apart.
- 1st dose at least 2 weeks before departure.
- 2nd dose 1 week after the 1st dose and at least 1 week before departure.
- Protection against traveller's diarrhea caused by ETEC starts 1 week after the second dose and will last for 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 renew the protection.
- If more than 5 years has passed since the last dose, complete primary immunization (2 doses) is recommended.

TO PREVENT CHOLERA:

Primary Immunization for adults and children 6 years and older:

- 2 doses orally at least 1 week apart.
- 1st dose at least 2 weeks before departure.
- 2nd dose 1 week after the 1st dose at least 1 week before departure.
- Protection against cholera starts 1 week after the second dose and will last for 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 renew the protection.
- If more than 5 years has passed since the last dose, complete primary immunization (2 doses) is recommended.

Primary Immunization for children 2 to 6 years:

3 doses orally at least 1 week apart and finishing at least 1 week before departure.

- 1st dose at least 3 weeks before departure; 2nd dose 1 week later; 3rd dose 1 week later and at least one week before departure.
- Protection against cholera starts after 1 week and will last for 6 months for children 2 to 6 years.
- If more than 6 weeks elapse between the 1st and 2nd dose, 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 renew the protection.
- If more than 5 years has passed since the last dose, complete primary immunization (3 doses) is recommended.

Important Information about Taking DUKORAL®:

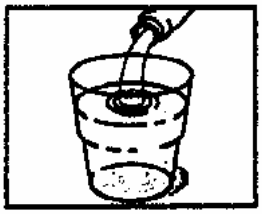
Do not eat or drink for 1 hour before and 1 hour after taking the vaccine.

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

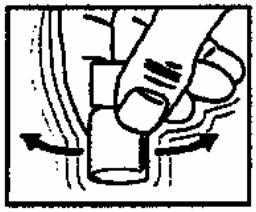
Use only cool water to mix the vaccine. (See 'How to Prepare DUKORAL®.') **Do not use any other liquid.**

How to Prepare DUKORAL®:

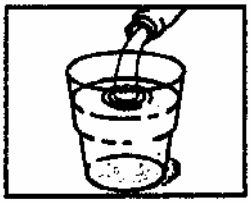
Mix the vaccine according to the directions below:



Step 1
Dissolve the powder from the sachet in 5 oz. (150 mL) of cool water.
For adults and children 6 years and older – proceed to Step 2.
For children 2 to 6 years – discard half the mixture and proceed to Step 2.



Step 2
Shake the small glass vial that contains the vaccine to mix it well.



Step 3
Open the vial and add the vaccine to the liquid in the glass. Stir well and drink immediately.
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 second dose is missed, it can be taken at any time within six weeks. Food and drink are to be avoided for 1 hour before and 1 hour after.

Overdosage

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

DUKORAL® [Oral, Inactivated Travellers' Diarrhea and Cholera 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 biotype and serotype. O-antigens as well as toxin B subunit will induce immunity. (8) Most ETEC strains produce an enterotoxin 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 ETEC, as well as cholera.

Pharmacodynamics

In clinical trials DUKORAL® has been shown to prevent TD caused by enterotoxigenic *E. coli* (9) (11) and cholera caused by *V. cholerae* O1 (classical and El Tor biotypes). (13) (14) Protection against ETEC diarrhea and cholera can be expected 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 ETEC: Protective efficacy with reference to all TD will vary depending on the prevalence of ETEC. There are considerable variations between different seasons and geographic areas. Protective efficacy against ETEC lasts about 3 months.

STORAGE AND STABILITY

Store at 2° to 8°C (35° to 46°F). DO NOT FREEZE.

The vaccine can be stored at room temperature (<27°C) for up to two weeks on one occasion only. After reconstitution the vaccine should be consumed within 2 hours.

The sodium hydrogen carbonate sachet may be stored separately at room temperature (<27°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 Travellers' Diarrhea and Cholera 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. 2.5 x 10^{10} vibrios
V. cholerae O1 Inaba El Tor strain, formalin inactivated	ca. 2.5 x 10^{10} vibrios

V. cholerae O1 Ogawa classic strain, heat inactivated	ca. 2.5 x 10^{10} vibrios
V. cholerae O1 Ogawa classic strain, formalin inactivated	ca. 2.5 x 10^{10} vibrios
Total	ca. 1 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.

Vaccine Information Service: 1-888-621-1146 or 416-667-2779. Business hours: 8 a.m. to 5 p.m. Eastern Time, Monday to Friday.

Full Product Monograph available on request or visit us at www.sanofipasteur.ca

Product Information as of November 2007.

Manufactured by:

SBL Vaccin AB

105 21 Stockholm, Sweden

Imported and Distributed by:

Sanofi Pasteur Limited

Toronto, Ontario, Canada R1-1107 Canada

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Oral, Inactivated Travellers' Diarrhea and Cholera 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. 2.5 x 10^{10} vibrios
V. cholerae O1 Inaba El Tor strain, formalin inactivated	ca. 2.5 x 10^{10} vibrios
V. cholerae O1 Ogawa classic strain, heat inactivated	ca. 2.5 x 10^{10} vibrios
V. cholerae O1 Ogawa classic strain, formalin inactivated	ca. 2.5 x 10^{10} 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 Travellers' Diarrhea and Cholera 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 Travellers' Diarrhea and Cholera Vaccine] has been shown to protect against travellers' diarrhea caused by enterotoxigenic *E. coli* (9) (11) and cholera caused by *V. cholerae* O1 (classical and El Tor biotypes). (13) (14)

Study Results - Efficacy

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-ETEC) during the initial 3 months of follow-up but demonstrated no protection thereafter. (11) Protective efficacy against clinically severe episodes of LT-ETEC was 86%. Results are shown in Table 1.

Table 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.

Table 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 travellers' diarrhea	23 (0.03)	16:30

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.

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 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 Travellers' Diarrhea and Cholera Vaccine] and 323 received a control buffer without vaccine. Adverse events reported following the first dose are shown in Table 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 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

Travellers' Diarrhea

Diarrhea is the most common medical problem affecting travellers from an area of more highly developed hygiene and sanitation infrastructure to a less developed one (16) (17) (e.g. Africa, Southeast Asia, Latin America, Mexico, Eastern and Southern Europe and the Carribean) A large number of enteric pathogens are much more prevalent in developing countries and the standards of water quality, sanitation and food preparation result in an increased risk of transmission. There are numerous opportunities in developing countries for food to become contaminated including the fertilization of crops with human fecal material, inadequate storage and transport of food, unreliable refrigeration, lack of pasteurization and unhygienic food handling practices. (18) Prevention strategies for TD 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. TD can be caused by both food and waterborne pathogens with most cases caused by food contaminated with

enterotoxigenic bacteria. ETEC is the most common cause of TD, being responsible for one-third to one-half of all diarrheal episodes in travellers to Africa, Asia and Latin America. Up to 50% of travellers from developed to developing countries can expect to have at least one episode of acute diarrhea during a 2-week stay, with 20% being confined to bed for a day. The most important determinant of risk is the travel destination and the type of travel. The attack rate is higher in adventure travellers (backpackers) due to food prepared in unsanitary conditions as well as in those staying at luxury hotels or resorts (4 star or higher) due to increased opportunities for food contamination. (17) Factors that may be associated with a higher probability of acquiring TD include adventurous eating habits, gastric hypochlorhydria including treatment with proton pump inhibitors (17) (20), gastrectomy, history of repeated severe TD, immunodeficiency diseases and the relative lack of gut immunity seen in younger persons. (18) Travellers with chronic illnesses (e.g., chronic renal failure, congestive heart failure, insulin dependent diabetes mellitus, inflammatory bowel disease) are at increased risk of serious consequences from TD. Diarrhea-induced dehydration is a concern in children and elderly persons.

Episodes of TD usually begin abruptly, either during travel or soon after returning home and are generally self-limited. TD can adversely affect the quality of a vacation or the success of a business trip. Concerns about the incidence of diarrhea in high-risk destinations may also impose limitations on the travellers' itineraries. The estimated economic impact of TD is significant. (18)

In practice, the majority of diarrheal episodes resolve, even without treatment, after a period of between hours and weeks. However, the incidence of persistent diarrhea of ≥30 days in travellers has been estimated at 1% to 3% (19) and studies have suggested that patients who experience an episode of infectious diarrhea may develop new irritable bowel syndrome (IBS) Post-infectious IBS may occur in up to 3% of persons who contracted travellers' diarrhea. (16) In a meta-analysis, the pooled risk estimated revealed a 7-fold increase in the odds of developing IBS following infectious gastroenteritis (21) and a recent study in travellers found a >5-fold (22) higher risk of developing new-onset IBS among travellers who experienced diarrhea during their journey, compared with travellers who did not experience diarrhea. Although analyses were made on data sets too small to achieve statistical significance, observations in this study suggest the possibility of a higher risk of IBS after use of antibiotics or antimotility agents during the episode of TD. There is no specific geographic association with persistent TD; the problem has been reported following travel to a wide range of developing countries. (22)

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 in 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. (24) (26) 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)

Recent 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) Most ETEC strains produce an enterotoxin 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 ETEC, as well as cholera. Protection against ETEC diarrhea and cholera can be expected about one week after the primary immunization series is completed. (1)

Mechanism of Action

DUKORAL® [Oral, Inactivated Travellers' Diarrhea and Cholera 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.

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 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 TD or an oral cholera vaccine.

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Full Product Monograph available on request or visit us at www.sanofipasteur.ca

Vaccine Information Service: 1-888-621-1146 or 416-667-2779. Business hours: 8 a.m. to 5 p.m. Eastern Time, Monday to Friday.

Product Information as of November 2007.

Manufactured by:

SBL Vaccin AB

105 21 Stockholm, Sweden

Imported and Distributed by:

Sanofi Pasteur Limited

Toronto, Ontario, Canada

R1-1107 Canada

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

DUKORAL®

Oral, Inactivated Travellers' Diarrhea and Cholera 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 travellers' diarrhea caused by enterotoxigenic *E. coli* (or ETEC) and/or cholera. The ETEC bacterium is the most common cause of travellers' diarrhea. DUKORAL® is used to help protect people who are travelling to an area where there is a risk of travellers' diarrhea caused by ETEC and/or cholera. 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 ETEC and cholera. After getting the vaccine, your body will make substances called antibodies, which fight the ETEC and cholera bacteria and toxins that cause diarrhea. If a vaccinated person comes into contact with ETEC or cholera 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 ETEC or cholera. Most people who take the vaccine will produce enough antibodies to protect them against diarrhea caused by 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 have an allergy to the vaccine or any ingredient in it.
- Do not give DUKORAL® to a child who has an allergy to the vaccine or any ingredient in it.
- Do not give DUKORAL® to a person who has a fever or serious illness. 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)
Each Sodium Hydrogen Carbonate sachet package contains:
Sodium hydrogen carbonate

What the important nonmedicinal ingredients are:
Each Sodium Hydrogen Carbonate sachet contains:
citric acid, sodium carbonate, sodium citrate, raspberry flavour, saccharin sodium.

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

What dosage forms it comes in:

DUKORAL® is a liquid vaccine that must be swallowed (taken orally). 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 should be dissolved in a glass of water – do not use any other liquid. The vaccine is mixed with this liquid. 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.**
- **Persons who have an infection 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 ETEC and cholera. It will not prevent diarrhea caused by other organisms. Travellers should always be careful when choosing food and should wash, peel or cook it themselves 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 1 hour before and 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 TRAVELLERS DIARRHEA CAUSED BY ETEC:

Primary Immunization for adults and children 2 years and older: 2 doses orally (by mouth) at least 1 week apart. Take the 1st dose 2 weeks before you leave for your trip. Take the 2nd dose 1 week after the first dose and at least 1 week before your trip. It takes 1 week after the last dose for protection to begin.

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

Booster: If you had your last dose of the vaccine between 3 months and 5 years before, one booster dose will renew your protection. If more than 5 years has passed since your last dose, you should have the complete primary immunization again.

TO PROTECT AGAINST CHOLERA:

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

Booster for adults and children over 6 years: If you had your last dose of the vaccine between 2 and 5 years before, one booster dose will renew your protection. If more than 5 years has passed since your last dose, you should have the complete primary immunization again.

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

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

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

Important Information about Taking DUKORAL®:

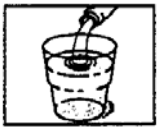
Do not eat or drink for 1 hour before and 1 hour after taking the vaccine.

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

Use only cool water to mix the vaccine. Do not use any other liquid.

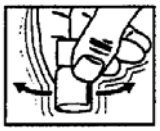
Follow the directions for proper mixing. It is important to follow these instructions to make sure the vaccine works.

How to take DUKORAL®:

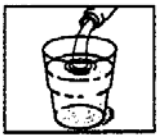


Step 1 - Dissolve the powder from the sachet package in 5 oz (150 mL) of cool water. Use only water.

For children 2 to 6 years: dissolve the powder in 5 oz (150 mL) of cool water and pour away half of the mixture before proceeding to Step 2.



Step 2 - Shake the glass vial that contains the vaccine to mix it well.



Step 3 – Open one vial and add the vaccine to the water and granule mixture in the glass. Stir well and drink immediately.

If you don't drink the mixture immediately, you should take it 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 travellers' diarrhea and cholera.

Make sure that you take the 2 doses at least one week apart (3 doses for children 2 to 6 years).

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).

If the second dose is missed, it can be taken at any time within 6 weeks. Food and drink must be avoided for 1 hour before and 1 hour after. Contact your doctor, nurse or pharmacist.

Overdose

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

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, due to the bicarbonate buffer used with this vaccine. 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 (below 27°C) for up to two weeks on one occasion only.

After mixing, the vaccine should be used 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, Health Canada collects information on serious and unexpected effects of vaccine(s). If you suspect you have had a serious or unexpected reaction to this vaccine you may notify

Health Canada by:
telephone: 613-952-6339
fax: 613-946-0224
By email: VAAES@phac-aspc.gc.ca

By regular mail:
The Vaccine Safety Unit
Immunization & Respiratory Infections Division
Centre for Infectious Disease Prevention & Control
Public Health Agency of Canada
PL 0602C Bldg #6, Tunney's Pasture
Ottawa, Ontario K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician, nurse or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at www.sanofipasteur.ca

You may also contact the vaccine producer, Sanofi Pasteur Limited, for more information. Telephone: 1-888-621-1146 (no charge) or 416-667-2779 (Toronto area). Business hours: 8 a.m. to 5 p.m. Eastern Time, Monday to Friday.

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