DUKORAL®

VACCINE AGAINST CHOLERA AND ETEC-DIARRHOEA
Oral suspension (vaccine) and effervescent granules (buffer).

COMPOSITION
I. Vaccine, one dose (3 ml) contains:
Vibrio cholerae O1 Inaba and Ogawa, classic and El Tor strains, approximately $1{,}25x10^{11}$ vibrios (heat/formalin inactivated), cholera toxin B subunit 1 mg, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium chloride, sterile water.

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

The vaccine is a whitish suspension in a single-dose glass bottle. 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.

HOW DOES THE VACCINE WORK?
The vaccine stimulates the immunological defence in the intestinal tract and gives protection against cholera and ETEC-diarrhoea. The ETEC-bacterium is one of the most common causes of "travellers' diarrhoea". The occurrence of ETEC varies a lot between different geographical areas. Satisfactory protection against cholera and ETEC diarrhoea can be expected about one week after basic immunisation is concluded.

INDICATION
Protection against cholera and ETEC-diarrhoea.
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: The vaccine is recommended for adults and children from 2 years of age who will be visiting areas posing a great risk of diarrhoeal illness caused by enterotoxigenic *Escherichia coli* (ETEC).

DO NOT USE DUKORAL®
- if you are allergic to any ingredient of the vaccine or to formaldehyde.
- if you have an acute stomach disorder or infection with fever (vaccination should be delayed).

SPECIAL WARNINGS AND PRECAUTIONS
Talk to your doctor before taking **DUKORAL®**
- if you take a medical treatment that affects the immune system
- if you have a disease of the immune system (including AIDS).

The vaccine may provide you with a lower level of protection than it does for people with healthy immune systems.
The vaccine does not provide complete protection and it is important to adhere to dietary and hygiene advice to avoid diarrhoeal diseases.

Children
Do not give this vaccine to children younger than 2 years since the protection has not been studied in this group.

Other medicines and DUKORAL®
Please tell your doctor if you are taking or have recently taken any other medicines.
Do not take other medicine starting 1 hour before until 1 hour after taking the vaccine.

Using DUKORAL® with food and drink
Avoid food and drink starting 1 hour before until 1 hour after the vaccination.

PREGNANCY AND BREASTFEEDING
If you are pregnant, think you may be pregnant or are planning to have a baby or are breast-feeding, ask your doctor before taking the vaccine.

DRIVING AND USING MACHINES
There are no reasons to suspect that **DUKORAL®** will affect your ability to drive or handle machines

DUKORAL® CONTAINS SODIUM
DUKORAL® contains approximately 1.1 g sodium per dose. Please take this into consideration if you are on a controlled sodium diet.

DOSAGE
Cholera
Adults and children from 6 years of age: The primary vaccination is 2 doses taken 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. For continuous protection, re-vaccination is recommended after 2 years.
Children of 2 to 6 years of age: The primary vaccination is 3 doses taken orally (by mouth) at least 1 week (up to 6 weeks) apart. Only half of the amount of the buffer solution should be mixed with the vaccine.
- Give the 1st dose to the child no later than 3 weeks before you leave for your trip.
- Give the 2nd dose to the child at least 1 week after the 1st dose.
- Give the 3rd dose at least one week after the 2nd dose and at least one week before your trip.

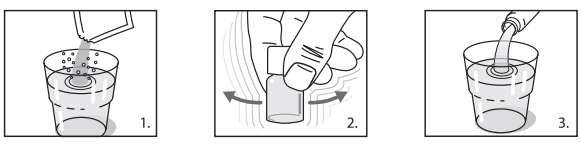
It takes about 1 week after the last dose for protection to begin. For continuous protection, re-vaccination is recommended after 6 months.

ETEC:
Adults and children: The primary vaccination is 2 doses taken 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.

INSTRUCTIONS
The vaccine is a whitish suspension supplied in a single-dose glass bottle. Each dose of vaccine comes with one sachet package that contains white effervescent granules of sodium hydrogen carbonate. The granules should be dissolved in a glass of cool water, and the resulting buffer solution should be mixed with the vaccine. It is important to use the buffer solution, as it protects the vaccine from the gastric acid.

Drink the vaccine within 2 hours after mixing with the buffer solution.



1. To prepare the buffer solution dissolve the effervescent granules in a glass of water (approx. 150 ml). Do not use any other liquid. *Children 2-6 years: pour away half of the solution.*
2. Shake the vaccine bottle (1 bottle = 1 dose).
3. Add the vaccine to the buffer solution. Mix well and drink the entire mixture. Drink the vaccine within 2 hours after mixing with the buffer solution. Avoid food and drink starting 1 hour before until 1 hour after the vaccination.

If you forget to take DUKORAL®
You can take the 2nd dose of **DUKORAL®** up to 6 weeks after the 1st dose (for cholera: children 2 to 6 years have to take 3 doses). If more than 6 weeks have passed, contact your doctor, pharmacist or nurse.

If you take more DUKORAL® than you should
If you take the doses less than one week apart, contact your doctor, pharmacist or nurse.
Because each bottle of **DUKORAL®** contains only one dose, overdosage is unlikely.
If you have taken more than one dose at one time, please contact your doctor, pharmacist or nurse.

POSSIBLE SIDE EFFECTS
Like all medicines, **DUKORAL®** can cause side effects, although not everybody gets them.
Contact a doctor immediately if you experience the following serious side effects:
- severe diarrhea with loss of water from the body
- serious allergic reactions causing swelling of the face or throat and breathlessness

Other side effects:
Uncommon side effects (may affect up to 1 in a 100 people)
- Diarrhoea, stomach pain, stomach cramps, gurgling stomach, bloated stomach, stomach gas and general stomach discomfort
- Headache

Rare side effects (may affect up to 1 in a 1,000 people)
- Fever
- Generally feeling unwell, feeling dizzy
- Nausea (feeling sick), vomiting, loss of /or poor appetite
- Swelling irritation inside the nose, and cough.

Very rare side effects (may affect up to 1 in a 10,000 people)
- Rash
- Sore throat, reduced sense of taste
- Fatigue/feeling tired
- Sweating, shivering
- Joint pain
- Difficulty in sleeping

Other side effects (frequency cannot be estimated from the available data)
- Flu-like symptoms, chestiness, chills, general pain, weakness
- Hives, itching
- Swelling of the lymph glands
- Numbness or pins and needles
- High blood pressure

STORAGE
Store at 2 °C–8 °C (in a refrigerator). Do not freeze.
Product in the unopened bottle and sachet, stored in the outer carton, is stable at temperatures up to 25°C for a period of 14 days. At the end of this period the product should be used or discarded.

After reconstitution the vaccine should be drunk within 2 hours.
Keep out of the reach and sight of children.
Do not use **DUKORAL®** after the expiry date which is stated on the carton.

MANUFACTURER
Valneva Sweden AB
105 21 Stockholm, Sweden.

PRODUCT NAME

DUKORAL®

DOSAGE FORMS AND STRENGTHS
Vibrio cholerae 01 Inaba classic strain, heat inactivated $31.25x10^9$ bacteria*;
Vibrio cholerae 01 Inaba El Tor strain, formalin inactivated $31.25x10^9$ bacteria*;
Vibrio cholerae 01 Ogawa classic strain, heat inactivated $31.25x10^9$ bacteria*;
Vibrio cholerae 01 Ogawa classic strain, formalin inactivated $31.25x10^9$ bacteria*;
Total $1.25x10^{11}$ bacteria*;
Recombinant cholera toxin B subunit (rCTB) 1 mg.
*bacterial count before inactivation
Oral suspension (vaccine) and effervescent granules (buffer). The vaccine is a whitish suspension in a single-dose glass bottle. The sodium hydrogen carbonate is supplied in a sachet as white effervescent granules with a raspberry flavour.
For a full list of excipients, see List of Excipients.

CLINICAL INFORMATION
INDICATIONS
Cholera: Active immunisation of 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: Active immunisation of adults and children from 2 years of age who will be visiting areas posing a great risk of diarrheal illness caused by enterotoxigenic *Escherichia coli* (ETEC), one of the most common causes of "travellers' diarrhea".
DUKORAL® should not replace standard protective measures. In the event of diarrhea measures of rehydration should be instituted.

DOSAGE AND ADMINISTRATION
Cholera: Primary immunisation: consists of 2 doses of vaccine for adults and children over the age of 6 years. Children from 2 to below 6 years of age should receive 3 doses. Doses are to be administered at intervals of at least 1 week. If more than 6 weeks elapse between doses, the primary immunisation course should be re-started.
Immunisation should be completed at least 1 week prior to potential exposure.
Booster dose: For continuous long-term protection, a single booster dose is recommended for adults after 2 years.
Children from 2–6 years of age should receive a booster dose after 6 months.
ETEC: Primary immunisation: For adults and children consists of 2 doses of vaccine at an interval of at least 1 week. If more than 6 weeks elapse between doses, basic immunisation should be re-started.
Satisfactory protection against cholera and ETEC diarrhoea can be expected about 1 week after basic immunisation is concluded.

Children below 2 years
DUKORAL® has been given to children between 1 and 2 years of age in safety and immunogenicity studies, but the protective efficacy has not been studied in this age group. Therefore, **DUKORAL®** is not recommended to be used in children below 2 years of age.

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

Method of Administration
The vaccine is intended for oral use. Before ingestion, the vaccine suspension should be mixed with a buffer (sodium hydrogen carbonate) solution.

The sodium hydrogen carbonate (buffer) is supplied as effervescent granules which should be dissolved in a glass of cool water (ca. 1.5 dl). Chlorinated water can be used.
The vaccine suspension should then be mixed with the buffer solution and drunk within 2 hours. Food and drink should be avoided 1 hour before and 1 hour after vaccination. Oral administration of other medicinal products should be avoided within 1 hour before and 1 hour after administration of **DUKORAL®**.
Children 2–6 years of age: half the amount of the buffer solution is poured away and the remaining part (approx. 75ml) is mixed with the entire contents of the vaccine bottle.

Valneva Sweden Intern EAN128 Pars 5 mm: SV40383B = 3832

Dukoral	PIL	Format: 170x440 mm	Technical approval: 24/SEP/2015; MÅB
Color:	black	Art.Nr.: SV40383B_SG	Good for printing: 24/SEP/2015; MÅB

CONTRAINDICATIONS
Hypersensitivity to the active substances, to any of the excipients or to formaldehyde.
Administration of **DUKORAL®** should be postponed for subjects suffering from acute gastrointestinal illness or acute febrile illness.

WARNINGS AND PRECAUTIONS
No clinical data on protective efficacy of **DUKORAL®** against cholera after administration of booster doses are available.
DUKORAL® confers protection specific to *Vibrio cholerae* serogroup O1. Immunisation does not protect against *V. cholerae* serogroup O139 or other species of *Vibrio cholerae*.
In subjects infected with HIV, limited data are available on immunogenicity and safety of the vaccine. Vaccine protective efficacy has not been studied in these subjects. Immunisation of HIV infected subjects could result in transient increases of viral load. **DUKORAL®** may not induce protective antibody levels in subjects with advanced HIV disease. However, an effectiveness study in a population with high HIV prevalence showed similar protection as in other populations.
Antibody response in vaccinees with endogenous or iatrogenic immunosuppression may be insufficient.
Formaldehyde is used during the manufacturing process and trace amounts may be present in the final product. Caution should be taken in subjects with known hypersensitivity to formaldehyde.
DUKORAL® contains approximately 1.1 g sodium per dose, which should be taken into consideration by patients on a controlled sodium diet.
The vaccine does not provide complete protection and it is important to adhere additionally to standard protective measures to avoid cholera.

As **DUKORAL®** is not the sole measure in prevention of cholera and ETEC diarrhoea, be cautious of the food and water intake during travel especially in regions with high disease risks.

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 should be avoided 1 hour before and 1 hour after vaccination.
Oral administration of other vaccines and medicinal products should be avoided 1 hour before and 1 hour after administration of **DUKORAL®**.
Preliminary results from a clinical study including a limited number of volunteers showed no interaction with the antibody response to **DUKORAL®** when a live oral vaccine (enterocapsules) against typhoid was given simultaneously with **DUKORAL®**. The immune response to live typhoid vaccine was not investigated in this study. Similarly, a yellow fever vaccine was given concomitantly with **DUKORAL®**, and there was no interaction observed with the immune response to the yellow fever vaccine. The immune responses to **DUKORAL®** were not studied. No other vaccines/ medicinal products, including oral polio vaccine and antimalarials, have been given simultaneously with **DUKORAL®** in clinical studies.

FERTILITY, PREGNANCY AND BREAST-FEEDING
No animal data on reproduction toxicity are available. Following careful benefit/risk assessment the vaccine may be administered during pregnancy and to breast-feeding women although no specific clinical studies have been performed to address this issue.
During a mass-vaccination campaign conducted in Zanzibar, 196 mothers had received at least one dose of **DUKORAL®** during pregnancy. There was no statistically significant evidence of a harmful effect of **DUKORAL®** exposure during pregnancy.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
There is no evidence of an effect on the ability to drive and use machines.

ADVERSE REACTIONS
Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of **DUKORAL®** based on the comprehensive assessment of the available adverse event information. A causal relationship with **DUKORAL®** usually cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in clinical practice.
The safety of **DUKORAL®** was assessed in clinical trials, including both adults and children, conducted in endemic and non-endemic countries for cholera and enterotoxigenic *Escherichia coli* (ETEC) producing heat-labile enterotoxin (LT). Over 94,000 doses of **DUKORAL®** were administered during the clinical trials. Evaluation of safety varied between trials with respect to mode of surveillance, definition of symptoms and time of follow-up. In the majority of studies adverse events were assessed by passive surveillance. The most frequently reported adverse reactions such as gastrointestinal symptoms including abdominal pain, diarrhea, loose stools, nausea and vomiting, occurred at similar frequencies in vaccine and placebo groups.

Frequency classification: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorder
Rare Loss of /or poor appetite
Very rare Dehydration

Nervous system disorders
Uncommon Headache
Rare Dizziness
Very rare Drowsiness, insomnia, fainting, reduced sense of taste

Respiratory, thoracic and mediastinal disorders
Rare Respiratory symptoms (including rhinitis and cough)

Gastrointestinal disorders
Uncommon Diarrhoea, abdominal cramps, abdominal pain, stomach/abdominal gurgling (gas), abdominal discomfort
Rare Vomiting, nausea
Very rare Sore throat, dyspepsia

Skin and subcutaneous tissue disorders
Very rare Sweating, rash

Musculoskeletal and connective tissue disorders
Very rare Joint pain

General disorders and administration site conditions
Rare Fever, malaise
Very rare Fatigue, shivers

Postmarketing data
Additional adverse reactions reported during post-marketing surveillance, are listed below.
The frequency cannot be estimated from the available data
Infections and infestations: Gastroenteritis
Blood and lymphatic system disorders: Lymphadenitis
Nervous system disorders: Paraesthesia
Vascular disorders: Hypertension
Respiratory, thoracic and mediastinal disorders: Dyspnea, increased sputum
Gastrointestinal disorders: Flatulence
Skin and subcutaneous tissue disorders: Urticaria, angioedema, pruritus
General disorders and administration site conditions: Pain, flu-like syndrome, asthenia, chills

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

PHARMACOLOGICAL PROPERTIES
PHARMACODYNAMIC PROPERTIES
ATC-code: J07A EO 1.
Mechanism of action
The 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. Dukoral is taken orally with bicarbonate buffer, which protects the antigens from the gastric acid. The vaccine acts by inducing antibodies against both the bacterial components and CTB. The antibacterial intestinal antibodies prevent the bacteria from attaching to the intestinal wall thereby impeding colonisation of *V. cholerae* O1. The anti-toxin intestinal antibodies prevent the cholera toxin from binding to the intestinal mucosal surface thereby preventing the toxin-mediated diarrhoeal symptoms.
The heat-labile toxin (LT) of enterotoxigenic ***E. coli*** (ETEC) is structurally, functionally and immunologically similar to CTB. The two toxins cross-react immunologically.
This means that **DUKORAL®** also will protect against ETEC diarrhoea. Cholera and ETEC infections are limited to the intestinal tract. It has been shown to be effective to administer the vaccine orally which will induce local immunity. Since the B subunit is acid labile, the vaccine is mixed with a buffering sodium hydrogen carbonate solution.
Efficacy against Cholera: Clinical results have revealed a protective efficacy against cholera of 80–85% for the first 6 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 6 months.
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% in the 6 months after the 3rd dose and 57% 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.
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.
Protective effectiveness against cholera was evaluated during two mass-vaccination campaigns conducted in Mozambique (December 2003 – January 2004) and Zanzibar (February 2009 – May 2010).
In the case-control study conducted during the mass vaccination campaign in Mozambique, protective effectiveness of 2 doses of **DUKORAL®** was 84% (95% CI: 43, 95, per-protocol analysis; p=0.005) for the initial 5 months of follow-up.
In the longitudinal cohort-analysis conducted during the mass-vaccination campaign in Zanzibar, protective effectiveness after 2 doses of **DUKORAL®** was 79% (95% CI, 47, 92) for a follow-up period of 15 months. In addition to the direct protection, it was shown that **DUKORAL®** provides significant indirect (herd) protection in the studied setting.

Efficacy against ETEC: Protective efficacy against ETEC diarrhoea is about 60%. Protective efficacy with reference to all kinds of tourist diarrhea will vary depending on the prevalence of ETEC. There are considerable variations between different seasons and geographic areas. (As an example: in a study the total incidence of diarrhoea, independent of cause, was among placebo treated Scandinavian tourists 31% compared to 24% of the vaccinated ones, i.e. 23% protective efficacy against all types of "travellers' diarrhea".)
Protective efficacy against ETEC is of comparatively short duration, lasting about 3 months.
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. Protective efficacy against clinically severe episodes of LT-ETEC was 86%
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.

PHARMACOKINETIC PROPERTIES
Not applicable

NON-CLINICAL INFORMATION
No preclinical safety testing with the vaccine has been conducted.

PHARMACEUTICAL PARTICULARS
LIST OF EXCIPIENTS VACCINE
Vaccine, 1 dose (3 ml) contains: Sodium dihydrogen phosphate, Disodium hydrogen phosphate, Sodium chloride, Water for injections.

Sodium hydrogen carbonate, one sachet (5.6 g) contains:
Sodium hydrogen carbonate, Citric acid, Sodium carbonate anhydrous, Saccharin sodium, Sodium citrate, Raspberry flavour.

INCOMPATIBILITIES
DUKORAL® should only be mixed with the supplied effervescent granules dissolved in water. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

SHELF LIFE
3 years. The expiry date is indicated on the packaging. After the effervescent granules have been dissolved in water and vaccine suspension has been added, the mixture shall be drunk within 2 hours.

STORAGE CONDITIONS
Keep refrigerated (2 ˚C–8 ˚C). Do not freeze.
Product in the unopened bottle and sachet, stored in the outer carton, is stable at temperatures up to 25°C for a period of 14 days. At the end of this period the product should be used or discarded.
Keep out of the sight and reach of children

NATURE AND CONTENTS OF CONTAINER
Oral suspension and effervescent granules, combined package. Each dose of vaccine is supplied with one sachet of sodium hydrogen carbonate. The vaccine suspension is filled in a volume of 3 ml in bottles (type I glass) with a rubber stopper (bromobutyl rubber) and a screw cap.
The effervescent granules are filled in sachets with an inner layer of polyester/LD-polyetylen and an outer layer of aluminium/LD-polyetylen.

INSTRUCTIONS FOR USE/HANDLING
Dissolve the effervescent granules in approximately 150ml of cool water. Shake the vaccine bottle gently and add the contents to the buffer solution. Mix well and drink the mixture.

Children 2 to 6 years of age: half of the buffer solution is poured away and the remaining part (approx. 75 ml) is mixed with the entire contents of the vaccine bottle.
Any unused product or waste material should be disposed of in accordance with local requirements.

PRODUCT LICENSE HOLDER
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SV40383B

Dukoral	PIL	Format: 170x440 mm	Technical approval: 24/SEP/2015; MÅB
Color:	black	Art.Nr.: SV40383B_SG	Good for printing: 24/SEP/2015; MÅB