ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dukoral suspension and effervescent granules for oral suspension
Cholera vaccine (inactivated, oral)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of vaccine suspension (3 ml) contains:

– A total of $1.25x10^{11}$ bacteria of the following strains:

Vibrio cholerae O1 Inaba, classical biotype (heat inactivated)	$31.25x10^9$ bacteria*
Vibrio cholerae O1 Inaba, El Tor biotype (formalin inactivated)	$31.25x10^9$ bacteria*
Vibrio cholerae O1 Ogawa, classical biotype (heat inactivated)	$31.25x10^9$ bacteria*
Vibrio cholerae O1 Ogawa, classical biotype (formalin inactivated)	$31.25x10^9$ bacteria*

– Recombinant cholera toxin B subunit (rCTB) 1 mg
(produced in *V. cholerae* O1 Inaba, classical biotype strain 213.)

* Bacterial count before inactivation.

Excipients:
Sodium dihydrogen phosphate dihydrate 2.0 mg, disodium hydrogen phosphate dihydrate 9.4 mg, sodium chloride 26 mg, sodium hydrogen carbonate 3600 mg, sodium carbonate anhydrous 400 mg, saccharin sodium 30 mg, sodium citrate 6 mg.

One dose contains approximately 1.1 g sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension and effervescent granules for oral suspension:
– Suspension for oral suspension
- Granules for oral suspension in a sachet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dukoral is indicated for active immunisation against disease caused by *Vibrio cholerae* serogroup O1 in adults and children from 2 years of age who will be visiting endemic/epidemic areas.

The use of Dukoral should be determined on the basis of official recommendations taking into consideration the variability of epidemiology and the risk of contracting disease in different geographical areas and travelling conditions.

Dukoral should not replace standard protective measures. In the event of diarrhoea measures of rehydration should be instituted.

4.2 Posology and method of administration

Posology

Primary vaccination schedule
The standard primary course of vaccination with Dukoral against cholera consists of 2 doses for adults and children from 6 years of age. Children 2 to below 6 years of age should receive 3 doses. Doses are to be administered at intervals of at least one week. If more than 6 weeks have elapsed between doses, the primary immunisation course should be re-started.

Immunisation should be completed at least 1 week prior to potential exposure to *V. cholerae* O1.

Booster dose
For continuous protection against cholera a single booster dose is recommended within 2 years for adults and children from 6 years of age, and within 6 months for children aged 2 to below 6 years. No clinical efficacy data has been generated on repeat booster dosing. However, immunological and duration of protection data suggest that if up to 2 years have elapsed since the last vaccination for adults and up to 6 months for children aged 2 to below 6 years a single booster dose should be given. If more than 2 years have elapsed since the last vaccination (more than 6 months for children aged 2 to below 6 years) the primary course should be repeated.

Children less than 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 less than 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 suspension should be mixed with the buffer (sodium hydrogen carbonate) solution. The sodium hydrogen carbonate is supplied as effervescent granules, which should be dissolved in a glass of cool water (approx. 150 ml). Chlorinated water can be used. The 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 to below 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 vial.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 or to formaldehyde.

Administration of Dukoral should be postponed for subjects suffering from acute gastrointestinal illness or acute febrile illness.

4.4 Special warnings and precautions for use

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.

In subjects infected with HIV, limited data are available on immunogenicity and safety of the vaccine. Vaccine protective efficacy has not been studied. 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.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

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 pregnant women had received at least one dose of Dukoral. There was no statistically significant evidence of a harmful effect of Dukoral exposure during pregnancy.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The safety of Dukoral was assessed in clinical trials, including both adults and children from 2 years of age, conducted in endemic and non-endemic countries for cholera and enterotoxigenic *Escherichia coli* (ETEC) producing heat-labile enterotoxin (LT). Over 94,000 doses of Dukoral were administered during the clinical trials. Evaluation of safety varied between trials with respect to mode of surveillance, definition of symptoms and time of follow-up. In the majority of studies adverse events were assessed by passive surveillance. The most frequently reported adverse reactions, such as

gastrointestinal symptoms including abdominal pain, diarrhoea, loose stools, nausea and vomiting, occurred at similar frequencies in vaccine and placebo groups.

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

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

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

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

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

Skin and subcutaneous tissue disorders
Very rare Sweating, rash

Musculoskeletal and connective tissue disorders
Very rare Joint pain

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

Adverse reactions from post-marketing surveillance

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

Infections and infestations: Gastroenteritis
Blood and lymphatic system disorders: Lymphadenitis
Nervous system disorders: Paraesthesia
Vascular disorders: Hypertension
Respiratory, thoracic and mediastinal disorders: Dyspnoea, increased sputum
Gastrointestinal disorders: Flatulence
Skin and subcutaneous tissue disorders: Urticaria, angioedema, pruritus
General disorders and administration site conditions: Pain, flu-like syndrome, asthenia, chills

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bacterial vaccines, ATC-code: J07AE01

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.

Efficacy against cholera

Efficacy against cholera was assessed in three randomised double-blind placebo-controlled clinical trials conducted in Bangladesh (endemic region) and in Peru (non-endemic region). The number of patients enrolled, dosage regimens and follow-up periods are shown in the following table.

Study location	**Year**	**Dosage regimen**	**Number (Age groups)**	**Follow up**
		Cholera		
Bangladesh	1985-88	3 doses at 6 week intervals	**89,152** (2-65 years)	6 months-5 years
Peru, military	1994	2 doses 7-11 days apart	**1,563** (18-65 years)	5 months
Peru, Pampas	1993-95	2 doses 2 weeks apart with a booster dose 1 year later	**21,924** (2-65 years)	2 years

In the Bangladesh field trial, protective efficacy of Dukoral in the overall population was 85% (95%CI: 56, 95, per-protocol analysis) for the initial 6 months of follow-up. Duration of vaccine protection differed by age, lasting for 6 months in children and for 2 years in adults (see table below). An exploratory analysis suggested that 2 vaccine doses seemed as effective as 3 doses in adults.

Table: Protective efficacy against cholera in the Bangladesh study (per-protocol analysis)

	Protective efficacy, % (95% CI)	
	Adults and children >6 year	Children 2-6 years
6 months	**76** (30, 92)	**100**
1st year	**76** (60, 85)	**44** (10, 65)
2nd year	**60** (36, 76)	**33** (-23, 64)

In the second trial, conducted in Peru and enrolling military recruits, the short-term protective efficacy against cholera after 2 vaccine doses was 85% (95%CI: 36, 97, per-protocol analysis). The third study, a field trial conducted in Peru, failed to show any protective efficacy against cholera during the first year. Following a booster dose 10-12 months after primary immunisation, the protective efficacy during the second year was 60.5% (95%CI: 28,79).

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.

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

Immunogenicity

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.

The vaccine induced intestinal antitoxin IgA responses in 70-100% of vaccinated subjects. Serum vibriocidal antibodies against the bacterial components were seen in 35-55% of vaccinated subjects and antitoxic antibodies in 78-87% of vaccinated subjects. 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.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

No preclinical safety testing with the vaccine has been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- suspension for oral suspension:

Sodium dihydrogen phosphate dihydrate
Disodium hydrogen phosphate dihydrate
Sodium chloride
Water for injections

- granules for oral suspension in a sachet ::

Sodium hydrogen carbonate

Citric acid
Sodium carbonate, anhydrous
Saccharin sodium
Sodium citrate
Raspberry flavour

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

After the effervescent granules have been dissolved in water and the vaccine suspension has been added, the mixture should be drunk within 2 hours.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.

Product in the unopened vial 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.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

The vaccine suspension is filled in a volume of 3 ml in vials (type I glass) with a rubber stopper (bromobutyl rubber) and a screw cap.
The effervescent granules are filled in an amount of 5.6 g in sachets with an inner layer of polyester/LD-polyethylene and an outer layer of aluminium/LD-polyethylene.

Each dose of vaccine is supplied as one vial of suspension together with one sachet of effervescent granules.

Pack sizes: 1x1 dose, 2x1 dose, 20x1 dose
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The effervescent granules should be dissolved in approximately 150 ml of cool water to get the buffer solution. The vaccine vial should be shaken gently and the vaccine suspension should then be added to the buffer solution and mixed well to get the colourless slightly opalescent oral suspension.
Children 2 to below 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 vial.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Valneva Sweden AB
S-105 21 Stockholm
Sweden
+46 (0)8 735 1000
infodukoral@valneva.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/263/001-003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 April 2004
Date of latest renewal: 25 March 2009

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substances

Valneva Sweden AB
SE-105 21 Stockholm
Sweden

Cobra BioPharma Matfors AB
Storjorden 2
SE-864 31 Matfors
Sweden

Name and address of the manufacturer responsible for batch release

Valneva Sweden AB
SE-105 21 Stockholm
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

DUKORAL – 1 dose package, 2x1 dose package, 20x1 dose package (outer sleeve)

1. NAME OF THE MEDICINAL PRODUCT

DUKORAL suspension and effervescent granules for oral suspension
Cholera vaccine (inactivated, oral)

2. STATEMENT OF ACTIVE SUBSTANCES

Active substances: 1 dose contains
- 31.25×10^9 bacteria* of each of the following *V. cholerae* O1 strains: Inaba classical biotype (heat inactivated), Inaba El Tor biotype (formalin inactivated), Ogawa classical biotype (heat inactivated), Ogawa classical biotype (formalin inactivated).
- Recombinant cholera toxin B subunit (rCTB) 1 mg.

*bacterial content prior to inactivation

3. LIST OF EXCIPIENTS

Contains sodium. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

3 ml of suspension in a vial and 5.6 g of effervescent granules in a sachet.
1 dose
2x1 dose
20x1 dose

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Mix suspension with buffer solution before drinking.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Valneva Sweden AB
105 21 Stockholm, Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/263/001 1 dose
EU/1/03/263/002 2x1 dose
EU/1/03/263/003 20x1 dose

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

DUKORAL

17. UNIQUE IDENTIFIER

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

DUKORAL – 20x1 dose package (inner carton for 20 vaccine vials)

1. NAME OF THE MEDICINAL PRODUCT

DUKORAL suspension
Cholera vaccine (inactivated, oral)

2. STATEMENT OF ACTIVE SUBSTANCES

Active substances: 1 dose contains
- $31.25x10^9$ bacteria* of each of the following *V. cholerae* O1 strains: Inaba classical biotype (heat inactivated), Inaba El Tor biotype (formalin inactivated), Ogawa classical biotype (heat inactivated), Ogawa classical biotype (formalin inactivated).
- Recombinant cholera toxin B subunit (rCTB) 1 mg.

*bacterial content prior to inactivation

3. LIST OF EXCIPIENTS

Contains sodium. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

3 ml of suspension in a vial.
20x1 dose.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Mix suspension with buffer solution before drinking.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Valneva Sweden AB
105 21 Stockholm, Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/263/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

DUKORAL – 20x1 dose package (inner carton for 20 sodium hydrogen carbonate sachets)

1. NAME OF THE MEDICINAL PRODUCT

Sodium hydrogen carbonate
Effervescent granules

2. STATEMENT OF ACTIVE SUBSTANCES

3. LIST OF EXCIPIENTS

Contains sodium. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

20 x 5.6 g

5. METHOD AND ROUTE(S) OF ADMINISTRATION

To be used with DUKORAL.
For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP MM/YYYY

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Valneva Sweden AB
105 21 Stockholm, Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/263/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

DUKORAL, vial label 1 dose

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

DUKORAL suspension
Oral use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP MM/YYYY

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (3 ml)

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Sodium hydrogen carbonate 5.6 g, sachet

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Sodium hydrogen carbonate effervescent granules
Oral use.

2. METHOD OF ADMINISTRATION

To be used with DUKORAL.
Read the package leaflet before use.

3. EXPIRY DATE

EXP MM/YYYY

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5.6 g

6. OTHER

Valneva Sweden AB, Sweden

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

DUKORAL suspension and effervescent granules for oral suspension
Cholera vaccine (inactivated, oral)

Read all of this leaflet carefully before you start using this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This vaccine has been prescribed for you only. Do not pass it on to others.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See Section 4.
- Make sure to mix the vaccine with buffer solution as described in this leaflet. See Section 3.

What is in this leaflet:

1. What Dukoral is and what it is used for

Dukoral is an oral vaccine against cholera that stimulates the immunological defence in the gut. The vaccine protects adults and children from 2 years of age against cholera.

Dukoral causes your body to produce its own protection against cholera. After getting the vaccine, your body will make substances called antibodies, which fight the cholera bacteria and toxin that cause diarrhoea.

2. What you need to know before you use Dukoral

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).

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 HIV infection).

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 breast-feeding
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.

3. How to use Dukoral

Always use this medicine exactly as described in this leaflet or as your doctor has told you. Check with your doctor if you are not sure.
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 within 2 years. If you had your last dose of vaccine less than 2 years ago a single dose will renew your protection. If more than 2 years have passed since you had the last vaccine dose, the primary vaccination (2 doses) should be repeated.

Children of 2 to below 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.

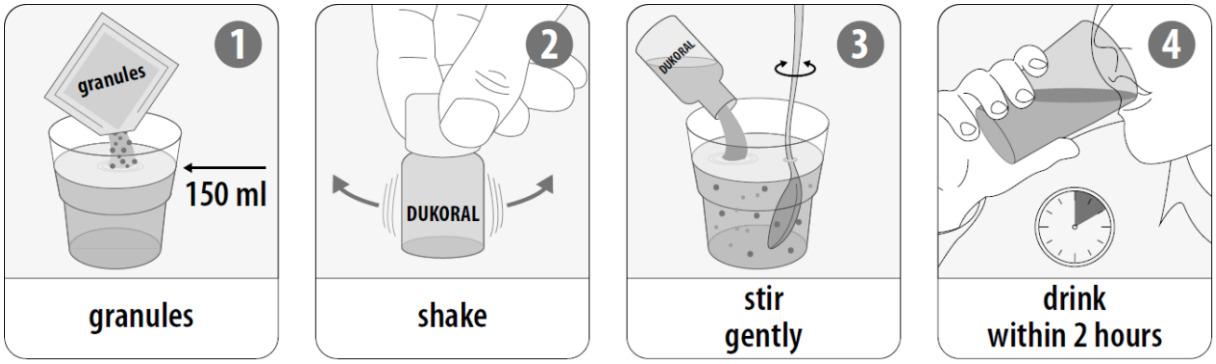
- Give the 1st dose to the child no later than 3 weeks before you leave for your trip.
- Give the 2nd dose to the child at least 1 week after the 1st dose.
- Give the 3rd dose at least one week after the 2nd dose and at least one week before your trip.

It takes about 1 week after the last dose for protection to begin.
For continuous protection, re-vaccination is recommended within 6 months. If less than 6 months have passed since the last vaccination a single dose will renew the protection. If more than 6 months have passed since the last vaccination, the primary vaccination (3 doses) should be repeated.

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

Drink the entire mixture within 2 hours after mixing with the buffer solution.

Instructions for use:



1. To prepare the buffer solution,dissolve the effervescent granules in a glass of cool water (approx. 150 ml) by gently stirring.
   Do not use any other liquid.
   For children of 2 to below6 years: pour away half of the buffer solution.

2. Shake the Dukoral® suspension vial (1 vial = 1 dose).

3. Pour the content of the Dukoral® suspension vial into the glass of buffer solution (see 1). Mix by gently stirring.

4. Drink the entire mixture within 2 hours. Avoid food and drink starting 1 hour before until 1 hour after drinking the mixture.

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 vial 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.

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

If you have any further questions on the use of this vaccine, ask your doctor, pharmacist or nurse.

4. 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 diarrhoea 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

Reporting of side effects
If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Dukoral

Keep this medicine out of the sight and reach of children.
Do not use Dukoral after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.
Store in a refrigerator (2°C – 8°C). Do not freeze.

Product in the unopened vial 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.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Dukoral contains
- The active substances are:
  31.25×10^9 bacteria* of each of the following *V. cholerae* O1 strains: Inaba classical biotype (heat inactivated), Inaba El Tor biotype (formalin inactivated), Ogawa classical biotype (heat inactivated), Ogawa classical biotype (formalin inactivated).
  Recombinant cholera toxin B subunit (rCTB) 1 mg.
  *bacterial content prior to inactivation

- The other ingredients in the vaccine suspension are sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium chloride and water for injections.

- The effervescent granules contain sodium hydrogen carbonate, citric acid, sodium carbonate, saccharin sodium, sodium citrate and raspberry flavour.

What Dukoral looks like and contents of the pack
Dukoral is presented as a suspension and effervescent granules for oral suspension. The suspension is a whitish suspension supplied in a vial. The effervescent granules are white with a raspberry flavour and are supplied in a sachet.

Dukoral is available in packs of 1, 2 and 20 doses. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu
This leaflet is available in all EU/EEA languages on the European Medicines Agency website.