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 25ºC 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

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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/.