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 1x10^{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 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.

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.

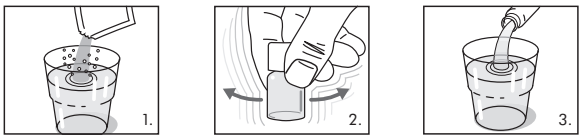
INDICATION
Protection against cholera and ETEC-diarrhoea.
Cholera: The vaccine is recommended for adults and children from 2 years of age who will be visiting areas with an ongoing or anticipated epidemic or who will be spending an extended period of time in areas in which cholera infection is a risk.
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).

SPECIAL WARNING
Vaccination should be postponed in case of acute illness.
Food and drink should be avoided 2 hours before and 1 hour after vaccination.

PREGNANCY AND LACTATION
The vaccine may be administered during pregnancy and to lactating women.

DOSAGE
Cholera: Basic immunisation comprises 2 doses of vaccine for adults and children over the age of 6. Children from 2 to 6 years of age should receive 3 doses. Doses are to be administered with an interval of 1–6 weeks.
Booster: For optimum long-term protection, a booster dose is recommended for adults after 2 years.
Children from 2 to 6 years of age should receive a booster dose after 6 months.
ETEC: Basic immunisation for adults and children comprises 2 doses of vaccine with an interval of 1-6 weeks between doses.

INSTRUCTIONS



1. Dissolve the sodium hydrogen carbonate in a glass of water (approx. 150 ml). *Children 2–6 years: pour away half of the solution.*
2. Shake the vaccine vial. (1 vial = 1 dose)
3. Add the vaccine to the sodium hydrogen carbonate solution. Mix well and drink the entire mixture.

SIDE EFFECTS
The most frequently reported side effects from clinical trials, such as gastrointestinal symptoms including stomach pain, diarrhoea, nausea and vomiting, occurred at similar frequencies in vaccine and placebo groups.
Uncommon side effects (reported by less than 1 in a 100 but more than 1 in a 1,000 people) include: diarrhoea, stomach pain, stomach cramps, gurgling stomach, bloated stomach, stomach gas and general stomach discomfort, headache.
Rare side effects (reported by less than 1 in a 1,000 but more than 1 in a 10,000 people) include:
high temperature, generally feeling unwell, nausea, vomiting, loss of/or poor appetite, runny nose, cough and dizziness.
Very rare side effects (reported by less than 1 in a 10,000 people) include: fatigue/feeling tired, shivering, severe diarrhoea, joint pain, sore throat, reduced sense of taste, sweating, being unable to sleep, general pain, hives or nettle rash, other types of rashes, flu-like symptoms, weakness, feeling cold, breathlessness, pins and needles, dehydration (loss of water from the body), swelling of face, high blood pressure, chestiness, itching, swelling of the lymph glands.

STORAGE
Store at 2°C – 8°C (in a refrigerator). Do not freeze.
After reconstitution the vaccine should be drunk within 2 hours.

MANUFACTURER
Crucell Sweden AB
105 21 Stockholm, Sweden.

Dukoral	PIL	Format: 170x250 mm		Technical approval: 25. Apr. 2013, AGJ
Color:	black	Art.Nr.	SV40383-_SG	Good for printing: 25. Apr. 2013, AGJ

3830

DUKORAL®

VACCINE AGAINST CHOLERA AND ETEC-DIARRHOEA
Oral suspension (vaccine) and effervescent granules (buffer)
- The most effective way to protect your patients against severe diarrhoea due to Cholera or ETEC.
- The first effective vaccine against Cholera and ETEC
- High level efficacy and excellent safety
- Easy administration: Oral vaccine

1. TRADE NAME OF THE MEDICINAL PRODUCT
DUKORAL™

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Vibrio cholerae 01 Inaba classic strain, heat inactivated ca. 2.5 x 10^{10} vibrios; *Vibrio cholerae* 01 Inaba EI Tor strain, formalin inactivated ca. 2.5 x 10^{10} vibrios; *Vibrio cholerae* 01 Ogawa classic strain, heat inactivated ca. 2.5 x 10^{10} vibrios; *Vibrio cholerae* 01 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

3. PHARMACEUTICAL FORM
Oral suspension (vaccine) and effervescent granules (buffer). 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.

4. CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Cholera: Active immunisation of adults and children 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 who will be visiting areas posing a great risk of diarrhoeal illness caused by enterotoxigenic *Escherichia coli* (ETEC), one of the most common causes of "tourist diarrhoea".

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Cholera: Basic immunisation comprises 2 doses of vaccine for adults and children over the age of 6. Children from 2 to 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, basic immunisation should be re-started.
Booster: For optimum long-term protection, a booster dose is recommended for adults after 2 years.
Children from 2 to 6 years of age should receive a booster dose after 6 months.
ETEC: Basic immunisation for adults and children comprises 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 one week after basic immunisation is concluded.

The sodium hydrogen carbonate buffer is supplied as effervescent granules which should be dissolved in a glass of water (ca. 1.5 dl). **DUKORAL™** should then be mixed with the sodium hydrogen carbonate solution and drink.
Children 2 to 6 years of age: half the amount of the sodium hydrogen carbonate solution is poured away and the remaining part is mixed with the vaccine.

4.3 CONTRA-INDICATIONS
None stated.

4.4 SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE
Vaccination should be postponed in cases of acute illness.
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.

4.5 INTERACTION WITH OTHER MEDICAMENTS 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 2 hours before and 1 hour after vaccination.

4.6 PREGNANCY AND LACTATION
The vaccine may be administered during pregnancy and to lactating women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Not applicable.

4.8 UNDESIRABLE EFFECTS
The most frequently reported side effects from clinical trials such as gastrointestinal symptoms including stomach pain, diarrhoea, nausea and vomiting, occured at similar frequencies with vaccine and placebo group. Uncommon side effects (reported by less than 1 in a 100 but more than 1 in a 1,000 people) include: diarrhoea, stomach pain, stomach cramps, gurgling stomach, bloated stomach, stomach gas and general stomach discomfort, headache.
Rare side effects (reported by less than 1 in a 1000 but more than 1 in a 10,000 people) include: high temperature, generally feeling unwell, nausea, vomiting, loss of/or poor appetite, runny nose, cough and dizziness.
Very rare side effects (reported by less than 1 in a 10,000 people) include: fatigue/feeling tired, shivering, severe diarrhoea, joint pain, sore throat, reduced sense of taste, sweating, being unable to sleep, general pain, hives or nettle rash, other types of rashes, flu-like symptoms, weakness, feeling cold, breathlessness, pins and needles, dehydration (loss of water from the body), swelling of face, high blood pressure, chestiness, itching, swelling of the lymph glands.

4.9 OVERDOSE
No cases of overdose have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES
ATC-code: J07A EO 1. The protection against cholera is specific for both biotype and serotype. O-antigens as well as toxin B subunit will induce immunity. Many antigenic components have been included in the vaccine in order to give a good protection. Most ETEC strains produce an enterotoxin which is structurally, pathophysiologically and immunologically similar to cholera toxin. This enterotoxin is neutralised by antibodies against cholera toxin subunit B.
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.
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 against ETEC diarrhoea is about 60%. Protective efficacy with reference to all kinds of tourist diarrhoea 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 "tourist diarrhea".) Protective efficacy against ETEC is of comparatively short duration, lasting about 3 months.

5.2 PHARMACOKINETIC PROPERTIES
None stated

5.3 PRECLINICAL SAFETY DATA
None stated

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS VACCINE
I 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

6.2 INCOMPATIBILITIES
DUKORAL™ should only be mixed with the supplied sodium hydrogen carbonate.

6.3 SHELF LIFE
3 years. The expiry date is indicated on the packaging. After the sodium hydrogen carbonate has been dissolved in water and vaccine added, the mixture shall be drunk within 2 hours.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Keep refrigerated (+2 ˚C and +8 ˚C). Do not freeze.

6.5 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 is tilled in a clear borosilicate glass vial with a rubber stopper and a screw cap. The sodium hydrogen carbonate is filled in sachets with an inner layer of polyester/LD-polyetylen and an outer layer of aluminium/LD-polyetylen.

6.6 INSTRUCTIONS FOR USE/HANDLING
Dissolve the sodium hydrogen carbonate in water. Shake the vaccine vial and add the contents to the sodium hydrogen carbonate solution. Mix well and drink the mixture.

7. MARKETING AUTHORISATION HOLDER
Johnson & Johnson Pte. Ltd.
2, International Business Park
#07-01, Tower One, The Strategy, Singapore 609930