PRODUCT MONOGRAPH

MUTACOL®
(Cholera Vaccine, Live, Oral, Attenuated, CVD103HgR)

A package of one single double-chambered aluminum foil sachet containing one dose of lyophilized powder for reconstitution. The sodium bicarbonate-ascorbic acid buffer is contained in chamber A while the CVD 103-HgR vaccine strain is contained in chamber B.

Active Immunizing Agent

Manufactured by:
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Action and Clinical Pharmacology

Mutacol® (Cholera Vaccine, Live, Oral, Attenuated, CVD103HgR) is a live attenuated vaccine for oral administration.

Vibrio cholerae is the etiological agent of cholera, an acute diarrheal disease. This vaccine will not afford protection against species of *Vibrio* other than 01 *V. cholerae* or against other bacteria that cause enteric disease. Mutacol Berna® Vaccine will not afford protection against 0139 *V. cholerae*.

There are less than 30 cases of cholera diagnosed per year in the United States (1,2) while 8 cases were identified in Canada during 1995 (3). All of these cases were contracted during travel outside of Canada (3). A small number of cholera cases have been contracted in the United States following the consumption of contaminated foodstuffs (4,5,6). No secondary spread of the disease was observed (7). Cholera is now considered to be endemic in most of Central and South America, sub-Saharan Africa and Southeast Asia (8). Antibiotics and oral rehydration solutions are used to treat cholera (7). Death

associated with cholera among European and North American travellers is rare. Upon ingestion, virulent stains of *V. cholerae* are able to pass through the stomach acid barrier and colonize the intestinal tract. *V. cholerae* present in the intestinal tract secrete cholera toxin which acts to stimulate fluid secretion, thereby resulting in the diarrhea characteristic of cholera. Possible mechanisms whereby disease may be prevented include evoking a local antibacterial and/or antitoxin immune response in the intestinal tract. Such local immunity may be induced by oral ingestion of *V. cholerae* undergoing an aborted infection. The ability of *V. cholerae* to cause disease and to induce a protective immune response is dependent upon colonization of the intestinal tract and secretion of cholera toxin. The *V. cholerae* CVD 103-HgR vaccine strain was attenuated by deletion of a gene segment from the bacterial chromosome which harbors the genetic information for the enzymatically active portion of the cholera toxin molecule (9). The non-active portion of the cholera toxin molecule is still synthesized. In addition, the insertion of a mercury-resistance marker into *hly*A gene appears to have diminished the ability of CVD 103-HgR to colonize the intestinal tract (10). Oral administration of the *V. cholerae* CVD 103-HgR strain is able to elicit a local intestinal and serum antibody response which recognizes native cholera toxin and wild type *V. cholerae* (10, 11, 12,13). Due to the inability of *V. cholerae* CVD 103-HgR to synthesize active cholera toxin, disease symptoms normally associated with *V. cholerae* infection are absent.

The efficacy of the CVD 103-HgR vaccine strain has been evaluated in a series of studies in which volunteers received either vaccine or placebo and subsequently ingested an amount of wild type 01 *V. cholerae* sufficient to cause disease symptoms. The results of these studies are summarized in Table 1.

Table 1. Protection against experimental cholera conferred following immunization with V. cholerae CVD 103-HgR

Biotype/ serotype of challenge strain[1]	No. of subjects	Day of challenge[2]	% protection against diarrhea[3]	P
Classical/Inaba	22	8	100	<0.01
	27	30	100	<0.01
	29	180	100	<0.01
El Tor/Inaba	14	30	62	0.06
El Tor/Ogawa	27	10	54	0.038
	19	30	64	<0.01

1 *V. cholerae* CVD 103-HgR is a Classical/Inaba strain.

2 Represents the number of days after immunization at which the challenge was performed.

3 Diarrhea was defined as the passage of two or more loose stools within 48 hrs. of at least 200 ml in volume, or a single loose stool of ≥300 ml in volume.

The degree of protection was influenced by the biotype and serotype of the challenge strain (10). Immunization with *V. cholerae* CVD 103-HgR conferred complete protection against a challenge strain of the same biotype/serotype (Classical/Inaba). Protection was evident 8 days after immunization. An undiminished level of protection was maintained for up to 6 months post-immunization. A lower level of protection was observed when a challenge strain with a heterologous biotype and/or serotype was used. It should be noted that immunization with *V. cholerae* CVD 103-HgR conferred complete protection against severe diarrhea (=2 L of total stool volume purged).

Additional challenge studies were performed with *V. cholerae* CVD 103, which is identical to *V. cholerae* CVD 103-HgR with the exception that it does not contain a mercury-

resistance marker. The protection afforded following immunization with *V. cholerae* CVD 103 and challenge approximately 1 month later with a Classical/Inaba, Classical/Ogawa or El Tor/Inaba strain was 87%, 82% and 67%, respectively (10). While *V. cholerae* CVD 103-HgR is excreted in the stool at a lower rate than *V. cholerae* CVD 103, the level of protection conferred when identical challenge strains were used was comparable (100% versus 87% for *V. cholerae* CVD 103-HgR and *V. cholerae* CVD 103, respectively, against a Classical/Inaba challenge, and 62% versus 67% against an El Tor/Inaba challenge).

The efficacy of the CVD 103-HgR vaccine strain has not been evaluated in cholera endemic areas. However, the above observations support the expectation that this vaccine will provide protection to recipients from non-cholera endemic areas such as Canada who travel to cholera endemic areas.

Indications and Clinical Use

Mutacol® (Cholera Vaccine, Live, Oral, Attenuated, CVD103HgR) is indicated for immunization of adults and children 2 years of age and older against disease caused by 01 *V. cholerae*. Results from clinical studies indicate that adults and children 2 years of age and older may be protected against cholera following the oral ingestion of 1 dose of this vaccine. Immunization should be completed at least 1 week prior to potential exposure to *V. cholerae*.

Routine immunization against cholera is not recommended in Canada (15). Selective immunization against cholera is recommended for travellers to areas of the world with a risk of exposure to cholera and for travellers to countries requiring evidence of cholera vaccination for entry (14).

Not all recipients of Mutacol® will be fully protected against cholera. Travellers should take all necessary precautions to avoid contact with or ingestion of potentially contaminated sources of food or water.

There is no evidence to support the use of cholera vaccine to control common source outbreaks or in the management of household contacts (6,7).

Mutacol® will not afford protection against enteric organisms other than *V. cholerae* (15).

An optimal booster dose has not yet been established. However, it is recommended that a booster dose be taken every 6 months under conditions of repeated or continued exposure to cholera (see Dosage and Administration section).

Cholera is present in many parts of the world. Travellers entering such areas are at risk to contracting cholera following the ingestion of contaminated food or water. Parenterally administered cholera vaccine has been shown to be effective at reducing the incidence of disease in such endemic areas. However, immunization with such vaccines is frequently accompanied by adverse reactions such as pain and/or swelling at the injection site, fever, malaise and headache.

Contraindications

Hypersensitivity to any component of the vaccine or the buffer.

Safety of Mutacol® (Cholera Vaccine, Live, Oral, Attenuated, CVD10-3HgR) has not been demonstrated in persons deficient in their ability to mount a humoral or cell-mediated immune response, due to either a congenital or acquired immunodeficient state including treatment with immunosuppressive or antimitotic drugs. The vaccine should not be administered to these persons regardless of the benefits.

Warnings

Mutacol® (Cholera Vaccine, Live, Oral, Attenuated, CVD10-3HgR) is not to be taken during an acute febrile illness or in the face of an acute gastrointestinal illness. Postpone taking the vaccine if persistent diarrhea or vomiting is occurring (see General Precautions). PHENYLKETONURICS: CONTAINS 17 MG OF PHENYL-ALANINE PER DOUBLE-CHAMBERED SACHET. This is due to the fact that Mutacol® is sweetened by aspartame (a phenylalanine derivative).

Precautions

General

Mutacol® (Cholera Vaccine, Live, Oral, Attenuated, CVD10-3HgR) should not be administered to persons during an acute febrile illness or acute gastrointestinal illness. The vaccine should not be administered to individuals receiving sulfonamides or antibiotics since these agents may be active against the vaccine strain and prevent a sufficient degree of multiplication to occur thus diminishing the immune response. Antimalarial prophylaxis with chloroquine should begin no sooner than 1 week after administration of Mutacol® since concomitant administration of this drug has been shown to decrease the immune response to the vaccine (16). The simultaneous administration of mefloquine or proguanil with Mutacol® has been shown not to significantly decrease the seroconversion rate (16). The concomitant administration of oral polio vaccine or yellow fever vaccine did not suppress the immune response elicited by Mutacol® (16). There is no reason to believe that simultaneous administration of parenteral vaccines or immunoglobulins with

Mutacol® will decrease vaccine efficacy. The administration of Mutacol® and Vivotif® (Typhoid Vaccine, Live, Oral, Attenuated Ty21a), enteric coated capsules, should be separated by at least 8 hours due to the fact that the buffer administered with Mutacol® may affect the transit of enteric coated capsules through the gastrointestinal tract. Mutacol® and Vivotif® L (Typhoid Vaccine, Live, Oral, Attenuated Ty21a) can be simultaneously administered safely without adversely affecting the immune response to either vaccine (17, 18). Mutacol® should be combined with the first dose of Vivotif® L as this dosing schedule has been shown to elicit an optimal immune response to both vaccines (17, 18). If taken together, a single sachet of Mutacol® and Vivotif® L should be reconstituted in the following way: The contents of the vaccine chamber (chamber B) of both vaccines are mixed with the contents of one buffer chamber (chamber A) in 100 mL (4 oz.) of cold or lukewarm water (see Dosage and Administration). Alternatively, Mutacol® and Vivotif® L can be administered separately with an interval of greater than 4 hours between vaccinations. This is to allow the gastric acidity to return to normal levels between dosing.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals with Mutacol® have not been performed as to carcinogenic potential, mutagenic potential or impairment of fertility.

Pregnancy

Animal reproduction studies have not been conducted with Mutacol®. It is not known whether Mutacol® can cause fetal harm when administered to pregnant women or can affect reproduction capacity Mutacol® should be given to a pregnant woman only if clearly needed.

Nursing mothers

There are no data to warrant the use of this product in nursing mothers. It is not known Mutacol® is excreted in human milk.

Pediatric Use

The safety of Mutacol® has not been established in children under 2 years of age. This product is therefore not recommended for use in children under 2 years of age.

Adverse Reactions

Several lots of Mutacol® (Cholera Vaccine, Live, Oral, Attenuated, CVD10-3HgR) have been evaluated in controlled clinical studies involving adults and children 2 to 9 years of age (10, 11, 12, 19). Objectively monitored side effects, e.g. abdominal pain, diarrhea, nausea, vomiting, fever, headache and skin rash, did not appear at a statistically higher frequency in the vaccinated group as compared to a placebo group (19). Reported adverse reactions include nausea, abdominal cramps and diarrhea.

Symptoms and Treatment of Overdosage

Mutacol® (Cholera Vaccine, Live, Oral, Attenuated, CVD10-3HgR) containing between 5 x 10^9 - 1 x 10^{10} viable vaccine organisms has been administered to several hundred adults and children 2 years of age and older (20, 21, 22, 23). This dosage was, at a minimum, 5-fold higher than the currently recommended dose. Objectively monitored adverse reactions e.g. abdominal pain, diarrhea, nausea, vomiting, fever, headache and skin rash, did not occur at a statistically higher rate among the vaccine recipients as compared to a placebo group.

Dosage and Administration

The sachet containing the buffer (Chamber A) and vaccine (Chamber B) should be inspected to ensure that the foil is intact. The vaccine is to be swallowed approximately one hour before a meal.

The vaccine is to be reconstituted in the following manner (see diagram on sachet). The sachet is to be folded along the solid black line and cut along the dotted line after insuring that the contents have been displaced to the bottom to prevent spillage. The contents of both chambers are to be emptied simultaneously into 100 ml (4 oz.) of cold or lukewarm water [temperature not to exceed body temperature, e.g. 37°C (98.6°F)]. Do not resuspend in milk, juice or in a carbonated beverage. Resuspend the sachet contents by gently mixing for 5-10 seconds. The vaccine should be swallowed as soon after mixing as possible. Not all recipients Mutacol® (Cholera Vaccine, Live, Oral, Attenuated, CVD10-3HgR) will be fully protected against cholera.

Travellers should take all necessary precautions to avoid contact with or ingestion of potentially contaminated food or water.

Pharmaceutical Information

Drug Substance and Composition

Mutacol® (Cholera Vaccine, Live, Oral, Attenuated, CVD10-3HgR) is a live attenuated vaccine for oral administration. The vaccine contains the attenuated strain *Vibrio cholerae* CVD 103-HgR and is manufactured by Berna Biotech Ltd. The vaccine strain is grown under controlled conditions in a medium containing casamino acids, yeast extract and mineral salts. The bacteria are collected by filtration, mixed with a stabilizer containing sucrose, ascorbic acid and amino acids and lyophilized. The lyophilized bacteria are mixed with lactose and aspartame and filled into one chamber of an aluminum foil sachet. Mutacol® is sweetened by aspartame (a phenylalanine derivative) and therefore contains 17 mg of phenylalanine. The other chamber of the sachet contains a sodium bicarbonate-ascorbic acid buffer which serves to neutralize gastric acid. The contents of the vaccine and buffer chamber are shown in Table 2.

Table 2: Contents of one double-chamber sachet of Mutacol®

Buffer Chamber (A)	
Sodium bicarbonate.....	2.4-2.9 g
Ascorbic acid.....	1.5-1.8 g
Lactose.....	0.18-0.22 g

Vaccine Chamber (B)

Viable *V. cholerae* CVD 103-HgR.....	2-10 x 10^8 colony-forming units
Non-Viable *V.cholerae* CVD 103-HgR.....	20 - 100 x 10^8 bacterial cells
Sucrose.....	1.4 - 30 mg
Amino acid mixture.....	0.15 - 3 mg
Ascorbic acid.....	0.06 - 1 mg
Aspartame.....	20 - 30 mg
Lactose.....	1.8 - 2.1 g

Stability and Storage Recommendations

Mutacol® (Cholera Vaccine, Live, Oral, Attenuated, CVD10-3HgR) is not stable when exposed to ambient temperatures. The vaccine should therefore be shipped and stored between 2°C and 8°C (35.6 - 46.4°F). Each package of vaccine shows an expiration date. This expiration date is valid only if the product has been maintained at 2 - 8°C (35.6-46.4°F). The product should be stored in a dry place and protected from light.

Reconstituted Solutions

For reconstitution instructions see Dosage and Administration above. The vaccine should be swallowed as soon after mixing as possible.

Booster Use

The optimum booster schedule for Mutacol® has not been determined. Efficacy has been shown to persist for at least 6 months. Furthermore, there is no experience with

Mutacol® as a booster in persons previously immunized with parenteral cholera vaccine. Despite these limitations, it is recommended that a booster dose be given every 6 months under conditions of repeated or continued exposure to cholera.

Availability of Dosage Form

Mutacol® (Cholera Vaccine, Live, Oral, Attenuated, CVD10-3HgR) is available in packages of one single double-chambered aluminum foil sachet containing one dose of vaccine. The sodium bicarbonate-ascorbic acid buffer is contained in Chamber A while the CVD 103-HgR vaccine strain is contained in Chamber B. The contents of each chamber require simultaneous reconstitution prior to oral administration.

Information for Patients

Vaccine potency is dependent upon storage under refrigeration [between 2°C and 8°C (35.6°F-46.4°F)]. The vaccine should be stored under refrigeration at all times. The vaccine should be ingested approximately 1 hour before a meal. It is essential that the buffer and vaccine be resuspended in cold or lukewarm water [temperature not to exceed body temperature, e.g. 37°C (98.6°F)]. Do not resuspend in milk, juice or in a carbonated beverage. It is essential that the buffer (Chamber A) and vaccine (Chamber B) be added to the liquid [approximately 100 ml (4 oz.)] at the same time and mixed for 5-10 seconds to yield a homogeneous suspension. The reconstituted vaccine should be swallowed as soon after reconstitution and mixing as possible.

PHENYLKETONURICS: CONTAINS 17 MG OF PHENYL-ALANINE PER DOUBLE-CHAMBERED SACHET. This is due to the fact that Mutacol® is sweetened by aspartame

(a phenylalanine derivative).

Pharmacology/Toxicology

No formal pharmacology/toxicology studies have been performed with V. cholerae CVD 103-HgR in animals except for the standard "General Safety Test", whereby the vaccine is administered to 5 mice and 2 guinea pigs by the intraperitoneal route to detect "abnormal toxicity". This test is performed on each lot of vaccine and buffer as part of the final release testing on the final product.

Historically, formal pharmacology/toxicology studies in animals have not been performed for vaccines for the following reasons. First, single and especially multiple dosing regimens can be confounded by the fact that administration of the test compound would, in essence, constitute an immunization and result in a subsequent induction of an antibody response. Therefore, clearance of the compound would be a balance between natural mechanisms and the formation of antibody-antigen complexes. Secondly, quantitating vaccine antigen in body fluids is made difficult by the fact that such antigen is rapidly cleared by macrophages and lymphocytes as part of the normal immune response mechanism.

Mutacol® is manufactured by Berna Biotech Ltd, Berne, Switzerland, and imported by Berna Products Corp., 1555 Bonhill Road, Unit #2, Mississauga, Ontario, Canada L5T 1Y5.

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