PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

VAXCHORA®

Cholera Vaccine, Live Attenuated, Oral

Each dose of VAXCHORA vaccine is supplied as a foil sachet of buffer and an accompanying foil sachet of the active component (lyophilized *V. cholerae* strain CVD 103-HgR), suspension for oral administration after reconstitution. Powder for oral suspension containing 4×10^8 to 2×10^9 colony forming units (CFU)/sachet of live attenuated *V. cholerae* vaccine strain CVD 103-HgR when reconstituted.

Therapeutic Classification: bacterial vaccines, cholera, live attenuated

ATC code: J07AE02

Manufactured by:
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

VAXCHORA® (Cholera Vaccine, Live Attenuated, Oral) is indicated for the active immunization against diarrheal disease caused by *Vibrio cholerae* serogroup O1 in persons 2 to 64 years of age travelling to cholera-affected countries.

The efficacy of VAXCHORA vaccine has not been evaluated in cholera endemic areas. However, it provides protection to vaccine recipients from areas not endemic for cholera, such as Canada, travelling to areas posing a threat of diarrheal disease caused by cholera. Onset of protection against cholera diarrhea can be expected one week after administration.

VAXCHORA vaccine should be used in accordance with official recommendations, taking into account the epidemiological variability and the risk of contracting diarrheal illness in different geographical areas and in different conditions of travel. VAXCHORA vaccine has not been shown to protect against *V. cholerae* serogroup O139 or other non-O1 serogroups, which are uncommon causes of disease.

The vaccine should not replace standard preventive hygiene measures. Travellers should take all necessary precautions to avoid contact with or ingestion of potentially contaminated food or water. Rehydration measures must be taken in the event of diarrhea.

1.1 Pediatrics

Pediatrics (< 2 years): The safety and efficacy of VAXCHORA vaccine have not been established in children younger than 2 years of age (see 14 CLINICAL TRIALS).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No data are available for individuals 65 years of age or older. However, this group can be expected to be at risk of more severe complications of disease if infected by cholera.

2 CONTRAINDICATIONS

Do not use in persons who have a history of severe allergic reaction (e.g., anaphylaxis) to any ingredient of VAXCHORA vaccine or to a previous dose of any cholera vaccine. For a complete listing of the ingredients (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

VAXCHORA vaccine is for oral use only.

Reconstitute before use (see 4.3 Reconstitution).

Avoid eating or drinking one hour before and one hour after taking VAXCHORA vaccine.

4.2 Recommended Dose and Dosage Adjustment

Adults and pediatric population 2 years and older

Administer a single oral dose of VAXCHORA vaccine a minimum of 10 days before potential exposure to cholera. For more information see section 4.3 Reconstitution.

VAXCHORA vaccine mimics natural infection, however duration of protection is unknown. The persistence of serum vibriocidal antibody response was assessed in a subset of adolescents 12-17 years of age where seroconversion was observed in 64.5% of participants two years post-vaccination (see 14.3 Immunogenicity). In the adult studies, significant increases in the percentage of anti-O1 lipopolysaccharide (LPS) IgA and IgG memory B cells and anti-cholera toxin IgG memory B cells were seen at 90 and 180 days after vaccination and increase in LPS IgA memory B cells was correlated with lower post cholera challenge stool volumes (see 10.2 Pharmacodynamics).

The safety and effectiveness of revaccination with VAXCHORA vaccine have not been established. The effectiveness of VAXCHORA vaccine has not been established in persons who have pre-existing immunity due to previous exposure to *V. cholerae* or receipt of any prior cholera vaccine.

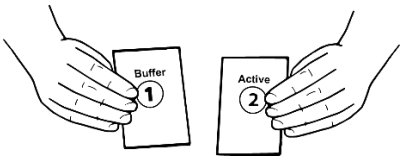
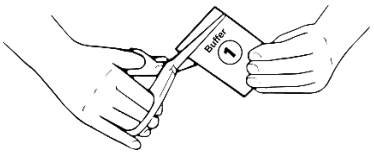
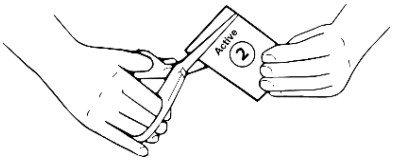
4.3 Reconstitution

1. **Oral Solutions:** Remove the carton from the refrigerator (see 11 STORAGE, STABILITY AND DISPOSAL). Remove and identify the 2 sachets:
   Sachet 1 contains "BUFFER COMPONENT OF VAXCHORA" and is black and white.
   Sachet 2 contains "ACTIVE COMPONENT OF VAXCHORA" and is blue and white.
2. Pour 100 milliliters (mL) of cold or room temperature (5°C-22°C) **bottled** water (purified, spring or sparkling [carbonated] into a clean cup. Do not use tap/faucet water, or any non-purified bottled water, other beverages, or liquids.
3. Use scissors to cut the top off sachet 1. NOTE: If the sachets are reconstituted in the improper order, the vaccine must be discarded (see 11 STORAGE, STABILITY AND DISPOSAL).
4. Empty sachet 1 (BUFFER COMPONENT) contents into cup. Effervescence, fizzing or bubbling will occur.
5. Using a stirrer, stir until the buffer component completely dissolves. For children ages 2 to 5 years, to reduce the volume they need to drink, discard half of the buffer solution after mixing.
6. Use scissors to cut the top of sachet 2 (ACTIVE COMPONENT).
7. Empty the contents of sachet 2 into the cup containing the buffer solution.
8. Stir for at least 30 seconds. The powder from sachet 2 may not dissolve completely. It will form a slightly cloudy suspension that may contain some white particles. If desired, no more than 4 grams (1 teaspoon) of sucrose (table sugar) or no more than 1 gram (1/4 teaspoon) of stevia sweeteners may be added and stirred into the suspension. DO NOT add other sweeteners or medicinal flavorings as this can reduce the effectiveness of the vaccine.
9. Drink the full contents of the cup within 15 minutes of reconstitution. Some residues may remain in the cup and should be discarded.
10. Clean used items and any spills with soap and hot water. If a spill occurs while stirring or drinking or there is residue (powder or liquid left behind from a stirring utensil, cup or other object) on the mixing surface, clean up spilled material or residue preferably with a disposable paper towel/cloth using hot water and soap. Discard the paper towel together with the sachets and any disposable items.

    Note: If there is a significant spill, dispose of the vaccine and contact your healthcare professional about acquiring a replacement dose.

11. Wash your hands thoroughly with soap and hot water.

See illustration for reconstitution below.

1  Remove the carton from the refrigerator. Identify the 2 sachets: sachet 1 contains “BUFFER COMPONENT OF VAXCHORA” and sachet 2 contains “ACTIVE COMPONENT OF VAXCHORA”.	2  Pour 100 milliliters (mL) of cold or room temperature (5ºC-22ºC) **bottled** water (purified, spring or sparkling [carbonated]) into a clean cup. Do not use tap/faucet water, or any non purified bottled water, other beverages, or other liquids.	3  Use scissors to cut the top off sachet 1 (BUFFER COMPONENT). Do not put your fingers into the sachet.
4  Empty the contents of sachet 1 into the water in the cup. Effervescence, fizzing or bubbling will occur.	5  Using a stirrer, stir until the powder completely dissolves. **For children ages 2 to 5 years only, pour out and discard half of the buffer solution.**	6  Use scissors to cut the top off sachet 2. Do not put your fingers into the sachet. Wash your hands if you touch the sachet contents, in order to reduce the chance of contamination.

7  Empty the contents of sachet 2 (ACTIVE COMPONENT) into the cup containing the buffer solution.	8  Stir for at least 30 seconds. The powder from sachet 2 may not dissolve completely. It will form a slightly cloudy suspension that may contain some white particles. If desired, no more than 4 g (1 teaspoon) of sucrose (table sugar) or 1 g (¼ teaspoon) stevia sweeteners may be added and stirred into the suspension.	9  Drink the full contents of the cup within 15 minutes of reconstitution. Some residues may remain in the cup and should be discarded.

4.4 Administration

For oral use only.

To protect the vaccine from the acidic environment of the stomach, it needs to be mixed with buffer. For instructions on reconstitution of VAXCHORA vaccine prior to administration see section 4.3 Reconstitution.

Avoid eating or drinking one hour before and one hour after taking VAXCHORA vaccine.

4.5 Missed Dose

Not applicable, as VAXCHORA vaccine is only one dose.

Consumption of less than a half dose may result in decreased protection. If less than half the dose is consumed, contact your healthcare professional about acquiring a replacement dose. Consideration may be given to repeating a full dose of VAXCHORA vaccine within 72 hours.

5 OVERDOSAGE

There have been reports of multiple doses of VAXCHORA vaccine being administered several weeks apart. The adverse reactions reported were comparable to those seen after the recommended dose.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Powder for oral suspension containing 4 × 10^8 to 2 × 10^9 CFU/dose of recombinant live attenuated *V. cholerae* vaccine strain CVD 103- HgR	*Active component sachet*: Ascorbic acid Hydrolyzed casein Lactose Sucrose *Buffer sachet*: Ascorbic acid Lactose Sodium bicarbonate Sodium carbonate

VAXCHORA vaccine is supplied in a carton containing one buffer sachet and one active component sachet (see 4 DOSAGE AND ADMINISTRATION).

The active component, sachet 2 contains 2 g of powder for oral suspension.

The buffer component, sachet 1, contains 4.5 g of effervescent powder.

The active ingredient sachet is made from four-ply multilayer foil containing an outer layer of paper, a layer of low-density polyethylene, a layer of aluminum foil and an inner layer of low-density polyethylene.

The buffer sachet is made from three-ply multilayer foil containing an outer layer of paper, a middle layer of aluminum foil and an inner layer of low-density polyethylene.

To help ensure the traceability of vaccines for immunization record-keeping as well as safety monitoring, it is recommended to record the time and date of administration, brand name and generic name of the vaccine, and the product lot number and expiry date.

7 WARNINGS AND PRECAUTIONS

General

VAXCHORA vaccine does not protect against *V. cholerae* O139 or other non-O1 serogroups of Vibrio, which are uncommon causes of disease.

Shedding and Transmission

VAXCHORA vaccine may be shed in the stool of recipients for at least 7 days. There is a theoretical risk of transmission of the vaccine strain to non-vaccinated close contacts (e.g., household contacts), see section 10.2 Pharmacodynamics. Use caution when considering whether to administer the vaccine to individuals with immunocompromised close contacts.

Gastrointestinal

In individuals with acute gastroenteritis, vaccination should be postponed until after recovery, because protection against cholera may be diminished. The degree of protection and the effects of vaccination in individuals with chronic gastrointestinal disease are unknown.

Immune

Altered Immunocompetence:

The safety and effectiveness of VAXCHORA vaccine have not been established in immunocompromised persons.

7.1 Special Populations

7.1.1 Pregnant Women

VAXCHORA vaccine is not absorbed systemically following oral administration.

Studies were not conducted in pregnant women. There is very limited experience with VAXCHORA vaccine during pregnancy in clinical trials. VAXCHORA vaccine should be used during pregnancy only if the potential benefits to the mother outweigh the potential risks, including those to the fetus.

7.1.2 Breast-feeding

It is unknown whether VAXCHORA vaccine is excreted in human milk. A risk to the breastfed child cannot be excluded.

7.1.3 Pediatrics

Use of VAXCHORA vaccine is supported by evidence from adequate and well-controlled studies in adults and children 2 years of age and older (see 8 ADVERSE REACTIONS and 14 CLINICAL TRIALS.)

The safety and effectiveness of VAXCHORA vaccine have not been established in children younger than 2 years.

7.1.4 Geriatrics

The safety and effectiveness of VAXCHORA vaccine have not been established in adults 65 years of age or older. However, this group can be expected to be at risk of more severe complications of disease if infected by cholera.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of VAXCHORA vaccine was evaluated in four randomized, placebo-controlled, multicenter clinical trials in adults (18 through 64 years of age) and one randomized, placebo-controlled, multicenter clinical trial in pediatrics (2 through 17 years of age) (see 14.1 Clinical Trial by Indication).

The most common adverse reactions among vaccine and placebo recipients overall were tiredness,

headache, nausea/vomiting, abdominal pain and lack of appetite. Common adverse reactions observed more frequently in VAXCHORA recipients versus placebo recipients included headache (28.9% vs 23.6%) in the adult trials, as well as tiredness (35.7% vs 30.7%), abdominal pain (27.8% vs 18.7%), and lack of appetite (21.4% vs 14.7%) in the pediatric trials. In addition, the adverse reaction of diarrhea was significantly higher for the adult VAXCHORA subjects 3.62% (115/3177) than the placebo group 1.63% (9/553), p=0.0140. For the pediatric study, the incidence of diarrhea was 1.5% (7/468) in vaccine recipients compared to 1.3% (1/75) in placebo recipients. This vaccine-associated diarrhea is typically mild and resolves spontaneously within 2 days in the majority of cases. There were no serious adverse events judged to be related to the administration of vaccine.

8.2 Clinical Trial Adverse Reactions – Adults

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of VAXCHORA vaccine was evaluated in four randomized, placebo-controlled, multicenter clinical trials. A total of 3235 adults 18 through 64 years of age received one dose of VAXCHORA vaccine and 562 received placebo (physiologic saline (N=551) or lactose (N=11)]. Overall, the mean age was 32.5 years; 53.8% of trial participants were female; 67.1% were White, 27.3% were Black or African American, 1.8% were Asian, 1.7% were multiracial, 1.3% were other, 0.6% were American Indian or Alaskan Native and 0.3% were Native Hawaiian or Pacific Islander. There were 9.3% Hispanic or Latino participants.

In a pooled analysis of the four clinical studies, 0.6% (20/3235) of VAXCHORA recipients and 0.5% (3/562) of placebo recipients reported a serious adverse event within 6 months post-vaccination. None of these events were considered to be related to vaccination.

Solicited Adverse Reactions

Adults 18 through 45 years of age received VAXCHORA vaccine in a multi-center, double-blind, randomized (8:1), placebo-controlled trial conducted in the United States and Australia (Study 3). The safety analysis set included 2789 VAXCHORA recipients. Solicited adverse reactions were recorded daily for 7 days following vaccination. Table 2 presents the frequency and severity of solicited adverse reactions observed within 7 days following receipt of VAXCHORA vaccine or placebo in Study 3.

Table 2 - Rates of Solicited Adverse Reactions Reported in VAXCHORA Trial Participants 18 to 45 Years of Age During 7 Days Post-Vaccination

	Study 3	
Adverse Reaction	**VAXCHORA** (N=2789)* %	**Placebo (Saline)** (N=350)* %
Gastrointestinal disorders		
Abdominal Pain	18.7	16.9
Mild	12.1	12.0
Moderate	6.2	5.0
Severe†	0.4	0.0
Diarrhea	3.9	1.2

	Study 3	
Adverse Reaction	**VAXCHORA** (N=2789)* %	**Placebo (Saline)** (N=350)* %
Mild	2.4	0.9
Moderate	0.7	0.3
Severe†	0.84	0.0
Lack of Appetite	16.5	16.6
Mild	11.7	12.2
Moderate	4.4	4.4
Severe†	0.3	0.0
Nausea/Vomiting	18.3	15.2
Mild	13.3	11.4
Moderate	4.7	3.8
Severe†	0.3	0.0
General disorders		
Fever	0.6	1.2
Mild	0.2	0.3
Moderate	0.3	0.9
Severe†	0.11	0.0
Nervous system disorders		
Headache	28.9	23.6
Mild	18.9	14.6
Moderate	9.6	8.8
Severe†	0.5	0.3
Tiredness	31.3	27.4
Mild	18.7	16.3
Moderate	12.0	9.9
Severe†	0.7	1.2

* N represents number of subjects who completed a memory aid.

† Severe category includes both grade 3 (severe) and grade 4 (potentially life-threatening) adverse events.

Grading scales are defined as follows:

Tiredness, Headache, Abdominal Pain, Nausea, Lack of Appetite: Mild = no interference with activity, Moderate = Some interference with activity, Severe = significant, prevents daily activity, Potentially Life Threatening = emergency room (ER) visit or hospitalization.

Vomiting: Mild = 1-2 episodes/24 hours, Moderate = >2 episodes/24 hours, Severe = requires intravenous hydration, Potentially Life Threatening = ER visit or hospitalization for hypotensive shock.

Diarrhea: Mild = 4 loose stools/24 hours, Moderate = 5 loose stools/24 hours, Severe = ≥6 loose stools /24 hours, Potentially Life Threatening = ER visit or hospitalization.

Fever: Mild = 38.0-38.4°C/100.4-101.1°F, Moderate = 38.5-38.9°C/101.2-102.0°F, Severe = 39.0-40.0°C/102.1-104.0°F, Potentially Life Threatening = >40.0°C/104.0°F.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The safety of VAXCHORA vaccine in children was evaluated in one randomized, placebo-controlled, multicenter clinical trial. A total of 468 children 2 through 17 years of age received one dose of VAXCHORA vaccine and 75 received placebo (physiologic saline). The mean age was 9.0 years; 51.6% were male; 59.5% were White, 31.3% were Black, 7.7% were multiracial, 0.9% were Asian, and 0.6% were American Indian/Alaskan Native. There were 8.7% Hispanic or Latino participants.

Solicited Adverse Reactions

Children 2 through 17 years of age received VAXCHORA vaccine in a multi-center, double-blind, randomized (6:1), placebo-controlled trial conducted in the United States (Study 5). The safety analysis set included 468 VAXCHORA recipients. Solicited adverse reactions were recorded daily for 7 days following vaccination. Table 3 presents the frequency and severity of solicited adverse reactions observed within 7 days following receipt of VAXCHORA vaccine or placebo in Study 5. There were no significant differences in solicited adverse reactions between the vaccine and placebo groups.

Table 3 - Rates of Solicited Adverse Reactions Reported in VAXCHORA Pediatric Trial Participants 2 to 17 Years of Age During 7 Days Post-Vaccination

	Study 5	
Adverse Reaction	**VAXCHORA** (N=468)* %	**Placebo (Saline)** (N=75)* %
Gastrointestinal disorders		
Abdominal Pain	27.8	18.7
Mild	22.4	14.7
Moderate	5.1	4.0
Severe[†]	0.2	0.0
Diarrhea	1.5	1.3
Mild	0.9	0.0
Moderate	0.0	1.3
Severe[†]	0.6	0.0
Lack of Appetite	21.4	14.7
Mild	16.5	12.0
Moderate	4.7	2.7
Severe[†]	0.2	0.0
Nausea	14.7	18.7
Mild	12.0	14.7
Moderate	2.6	4.0
Severe[b]	0.2	0.0
Vomiting	3.8	4.0

	Study 5	
Adverse Reaction	**VAXCHORA** (N=468)* %	**Placebo (Saline)** (N=75)* %
Mild	2.6	2.7
Moderate	1.1	1.3
Severe[b]	0.2	0.0
General disorders		
Fever	2.1	2.7
Mild	0.4	0.0
Moderate	0.4	1.3
Severe[†]	1.3	1.3
Nervous system disorders		
Headache	27.4	25.3
Mild	20.7	22.7
Moderate	6.0	2.7
Severe[†]	0.6	0.0
Tiredness	35.7	30.7
Mild	24.6	22.7
Moderate	10.7	6.7
Severe[†]	0.4	1.3

* N represents number of subjects who completed a memory aid.

[†] Severe category includes both grade 3 (severe) and grade 4 (potentially life-threatening) adverse events. Grading scales are the same as footnoted for Table 2.

Overall, VAXCHORA vaccine was well-tolerated in the pediatric population, with a solicited event profile very similar to adults.

8.3 Less common clinical trial adverse reaction

Less common clinical trial adverse events reported in <1% of clinical subjects include:

Gastrointestinal disorders: abdominal tenderness, ulcerative proctitis, rectal haemorrhage, oesophageal burning, gastritis, stomatitis, anal pruritis

Skin and subcutaneous tissue disorders: angioedema

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

No trends between pre-vaccination values on Day 1 and post-vaccination values on Day 7 were observed in the clinical safety laboratory evaluations in the Phase I trial.

8.5 Post-Marketing Adverse Reactions

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

Gastrointestinal disorders: abdominal discomfort

General disorders: chest pain, chills, feeling hot, malaise, pain

Musculoskeletal and connective tissue disorders: arthralgia, mobility decreased, myalgia, pain in extremity

Nervous system disorders: dizziness

Psychiatric disorders: anxiety

Skin and subcutaneous tissue disorders: hyperhidrosis

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Do not administer concomitantly with antibiotics or chloroquine. When VAXCHORA vaccine is taken with Vivotif®, typhoid vaccine Ty21a (gastro-resistant capsules) there should be an interval of 2 hours between the administration of VAXCHORA and Vivotif vaccines.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions.

Table 4 - Established or Potential Drug-Drug Interactions

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Vaccines	CT	Data from studies with a similar product indicate that the concomitant administration of oral polio vaccine or yellow fever vaccine did not affect the immune response produced by the cholera vaccine.	
Vaccines	T	The effects of concomitant administration of hepatitis A, hepatitis B, Japanese encephalitis, meningococcal, monkeypox, influenza, measles-mumps-rubella, tetanus-diptheria-pertussis, polio, varicella or rabies vaccines in subjects treated with VAXCHORA vaccine have not been studied.	Clinical outcome can not be determined since there is no information available on interaction with other vaccines.

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Vivotif	T	The buffer administered with VAXCHORA vaccine may affect the transit of the capsules through the gastrointestinal tract.	There should be an interval of 2 hours between the administration of VAXCHORA vaccine and Vivotif®, typhoid vaccine Ty21a (gastro-resistant capsules).
Antibiotics	T	These agents may be active against the vaccine strain and prevent a sufficient degree of multiplication to occur in order to induce a protective immune response.	Avoid concomitant administration of VAXCHORA vaccine with systemic antibiotics. Do not administer VAXCHORA vaccine to patients who have received oral or parenteral antibiotics within 14 days prior to vaccination. Oral or parenteral antibiotics should be avoided for 10 days following vaccination with VAXCHORA vaccine.
Antimalaria Prophylaxis - Chloroquine	CT	Data from a study with a similar product indicate that the immune responses to VAXCHORA vaccine may be diminished when it is administered concomitantly with chloroquine.	Administer VAXCHORA vaccine at least 10 days before beginning antimalarial prophylaxis with chloroquine

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

The vaccine is acid-labile and is administered with a buffer. Avoid eating and drinking for 1 hour before and 1 hour after taking VAXCHORA vaccine as this may interfere with the protective effect of the buffer (see 4.4 Administration].

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

VAXCHORA (Cholera Vaccine, Live Attenuated, Oral) is a live, attenuated bacterial vaccine suspension for oral administration containing the *V. cholerae* strain CVD 103-HgR. CVD 103-HgR was constructed from the serogroup O1 classical Inaba strain 569B by deleting the catalytic domain sequence of both

copies of the *ctxA* gene, which prevents the synthesis of the toxic subunit A of cholera toxin, thus preventing synthesis of active cholera toxin (CT). This attenuated strain remains able to synthesize the immunogenic non-toxic B subunit of CT (encoded by the *ctxB* gene). In addition, a marker was inserted into the hemolysin gene locus (*hlyA*) to enable differentiation of the vaccine strain from wild type *V. cholerae* O1. CVD 103-HgR elicits local intestinal and serum vibriocidal antibody and memory B cell responses which recognizes native cholera toxin and wild type *V. cholerae*. Due to the inability of CVD 103-HgR to synthesize active cholera toxin subunit A, diarrheal disease normally associated with *V. cholerae* infection is absent.

After reconstitution, VAXCHORA vaccine contains 4 x 10^8 to 2 x 10^9 colony forming units (CFU) of live attenuated *V. cholerae* CVD 103-HgR. The resulting suspension should be slightly cloudy and may contain white particulates. The ability of *V. cholerae* to cause diarrheal disease and to induce a protective immune response is dependent upon colonization of the intestinal tract and secretion of cholera toxin. VAXCHORA vaccine is able to elicit a local intestinal and serum vibriocidal antibody and memory B cell response which recognizes native cholera toxin and wild type *V. cholerae*. Although VAXCHORA vaccine contains live attenuated cholera bacteria that replicate in the gastrointestinal tract of the recipient, the specific immune mechanisms conferring protection against cholera following receipt of the vaccine have not been determined. However, rises in serum vibriocidal antibody 10 days after administration of VAXCHORA vaccine were associated with protection in a human challenge study (Study 2) (see section 14.3 Immunogenicity).

10.2 Pharmacodynamics

Not applicable

10.3 Pharmacokinetics

Duration of Effect

The duration of protection is unknown. However, persistence of immune response was evaluated in three phase 3 randomized placebo-controlled clinical studies in adults of 18 to 64 years of age (see section 14.1 Clinical Trial by Indication). Geometric mean titers (GMTs) of serum vibriocidal antibodies in vaccinated subjects were significantly higher than the respective GMTs of placebo recipients at 90 and 180 days after immunization in all age groups. Persistence of vibriocidal antibody response was assessed in a subset of adolescents ages 12-17 years in Study 5 where seroconversion was observed in 64.5% of participants two years post-vaccination (see section 14.3 Immunogenicity). In the adult studies, significant increases in the percentage of anti-O1 lipopolysaccharide (LPS) IgA and IgG memory B cells and anti-cholera toxin IgG memory B cells were seen at 90 and 180 days after vaccination and increase in LPS IgA memory B cells was correlated with lower post cholera challenge stool volumes.

The duration of shedding of the vaccine strain is unknown. However, shedding of the vaccine strain was evaluated in the first 7 days post-vaccination in a study of 53 healthy adult vaccine recipients (Study 1). VAXCHORA vaccine was shed in the stools of 11.3% [95% CI 4.3%, 23.0%] of vaccine recipients on any day through 7 days post-vaccination. During the 7 days post-vaccination, the proportion of subjects shedding was highest on day 7 (7.5% [95% CI 2.1%, 18.2%]).

11 STORAGE, STABILITY AND DISPOSAL

Store VAXCHORA buffer component and active component sachets refrigerated at 2°C to 8°C.

Protect from light and moisture.

Sachets should be kept refrigerated but may be used if left at or below 25°C up to 12 hours prior to reconstitution; when out of refrigerated storage, sachets should not be exposed to temperatures above 25°C.

If the integrity of the packet has been compromised, or if the vaccine and/or buffer shows signs of yellowing and clumping, then the vaccine/buffer should be discarded.

The reconstituted vaccine forms a white to off-white cloudy suspension that may contain some white particulates. The dose should be administered within 15 minutes of reconstitution with **bottled** water (purified, spring or sparkling [carbonated]).

Note: if the sachets are reconstituted in the incorrect order, the vaccine must be discarded (see 4.3 Reconstitution].

Clean all used items and surfaces with soap and hot water. Discard sachets and any disposable item in the garbage (see 4.3 Reconstitution).

12 SPECIAL HANDLING INSTRUCTIONS

Inform vaccine recipients that VAXCHORA vaccine is a live attenuated vaccine and has the potential for transmission of the vaccine strain to close contacts (e.g., household contacts). For at least 14 days following vaccination, VAXCHORA recipients should wash their hands thoroughly after using the bathroom and before preparing or handling food.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: V. cholerae CVD 103-HgR

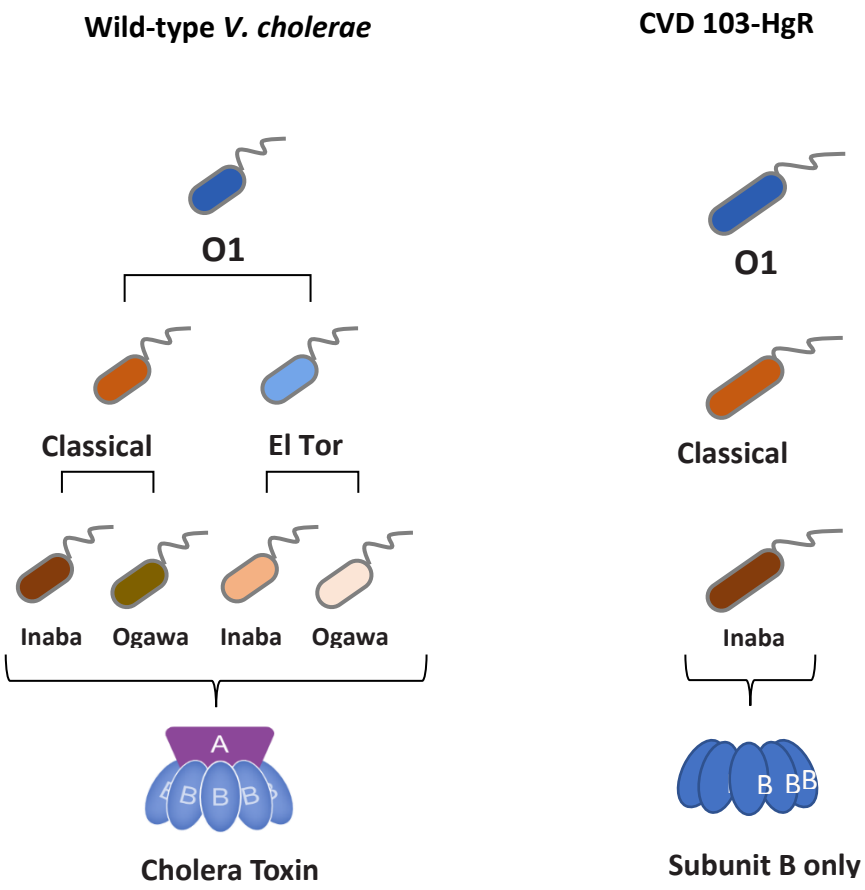
Chemical name: N/A

Molecular formula and molecular mass: N/A

Structural formula: The CVD 103-HgR strain developed from the *V. cholerae* classical Inaba O1 strain 569B is characterized by two prominent genetic modifications generated using standard methods and introduced into the chromosomes by a marker exchange technique.

Physicochemical properties: VAXCHORA (Cholera Vaccine, Live Attenuated, Oral) is a live, replication-competent recombinant, attenuated cholera vaccine, comprising the *V. cholerae* serotype O1 Inaba CVD 103-HgR strain. Attenuation is effected by the deletion of a substantial portion of the catalytic subunit A of the two copies of the cholera enterotoxin gene (*ctxA*). A mercury resistance marker is inserted within the hemolysin A (*hlyA*) locus to allow the vaccine strain to be distinguished from the wild-type *V. cholerae* O1.

Figure 1 - Schematic Representation of CVD 103-HgR Derived from Wild-Type *V. Cholerae*



Product Characteristics:

The vaccine drug product is formulated as a white to beige powder preparation for oral administration and is stabilized with a mixture of sugars and filled into sachets. The buffer component is formulated by blending together sodium bicarbonate (a gastric acid neutralizer), sodium carbonate (a buffer), ascorbic acid (a buffer and water chlorine neutralizer) and anhydrous lactose (a manufacturing flow aid) and filled into sachets. VAXCHORA® (Cholera Vaccine, Live Attenuated, Oral) consists of one buffer component sachet and one active component sachet packaged into individual single dose cartons for distribution. The reconstituted vaccine is administered orally after reconstitution. After reconstitution, VAXCHORA vaccine contains 4 x 10^8 to 2 x 10^9 colony forming units (CFU) of live attenuated *V. cholerae* CVD 103-HgR. The resulting suspension should be slightly cloudy and may contain white particulates.

14 CLINICAL TRIALS

14.1 Clinical Trial by Indication

Table 5 - Summary of Patient Demographics for Clinical Trials

Study #	Trial design	Trial Objective	Dosage, route of administration and duration	Study subjects (n) *(subjects receiving vaccine/placebo)*	Mean age (Range)	Sex
1	Randomized, double-blind, placebo-controlled	Phase 1 Safety, Immunogenicity, Kinetics (Shedding)	4.43 x 10^8 CFU/dose; oral single dose; 8 months	n = 66 vaccine = 55 *(vaccine = 55)* placebo = 11 *(placebo = 11)*	29.9 (21-48) years	M =33 F = 33
2	Randomized, double-blind, placebo-controlled	Phase 3 Efficacy (Challenge), Immunogenicity	5 x 10^8 CFU/dose; oral single dose; 10.5 months	n = 197 vaccine = 95 *(vaccine = 95)* placebo = 102 *(placebo = 102)*	31.0±7.79 (18-45) years	M = 124 F = 73
3	Randomized, double-blind, placebo-controlled	Phase 3 Lot Consistency, Safety, Immunogenicity	1 x 10^9 CFU/dose; oral single dose; 9.3 months	n = 3146 vaccine = 2795 *(vaccine = 2789)* placebo = 351 *(placebo = 350)*	29.9±7.76 (18-45) years	M = 1423 F = 1723
4	Randomized, double-blind, placebo-controlled	Phase 3 Safety, Immunogenicity, Bridging (older adults)	1 x 10^9 CFU/dose; oral single dose; 9.3 months	n = 398 vaccine = 299 *(vaccine = 296)* placebo = 99 *(placebo = 99)*	53.8±5.04 (46-64) years	M = 182 F = 216
5	Randomized, double-blind, placebo-controlled	Phase 4 Safety, Immunogenicity, Bridging (Pediatric)	1 x 10^9 CFU/dose; oral single dose; 25 months	n = 550 vaccine = 471 *(vaccine = 468)* placebo = 79 *(placebo = 75)*	9.0±4.7 (2-17) years	M = 286 F = 264

M=male, F=female

One Phase 1, three Phase 3 (a cholera challenge study demonstrating protective efficacy, a lot-to-lot consistency study, a study in older adults) and one Phase 4 trial in the pediatric population were conducted (Table 5). Each clinical trial used a single oral dose of VAXCHORA vaccine, and all studies were randomized, double-blind, and placebo-controlled. Safety and immunogenicity were assessed in each trial according to predefined Statistical Analysis Plans. Safety follow-up was for 6 months post-vaccination in each trial, and vaccine reactogenicity was solicited using a memory aid for 7 days post-vaccination.

<u>Efficacy against cholera challenge</u>

VAXCHORA efficacy against cholera was demonstrated in a randomized double-blind, saline placebo-controlled *V. cholerae* challenge study conducted in 197 healthy adult volunteers in the US (Study 2).

The mean age was 31 years (range 18 to 45, 62.9% male, 37.1% female) and a subset of VAXCHORA vaccine or placebo recipients were randomized to be challenged with live *V. cholerae* at either 10 days post-vaccination (n=68) or 3 months post-vaccination (n=66). Among subjects selected for either challenge cohort, more males were challenged in the vaccine group (76.5%) compared to the placebo group (57.6%). The majority (70.9%) of the challenge population was Black, 25.4% were White, 0.7% were American Indian/Alaskan Native, 0.7% were Asian, and 2.2% were other. There were 3.7% Hispanic or Latino participants. Overall, 56.0% of challenged subjects had blood type O.

Immunogenicity

In addition to study 2, three additional studies evaluated immunogenicity: a large trial in 3146 healthy adults ages 18 to 45 years (mean age 29.9, 45.2% male, 54.8% female) (study 3); a trial in 398 healthy older adults ages 46 to 64 years (mean age 53.8, 45.7% male, 54.3% female) (study 4); and a pediatric trial in healthy subjects ages 2-17 years (study 5) (Table 5).

A vibriocidal antibody assay was used to measure serum levels of neutralizing antibodies against the vaccine strain (classical Inaba). In the challenge study, serum vibriocidal antibody (SVA) seroconversion, defined as a 4-fold rise in titers over baseline at day 10, strongly correlated with protection against cholera diarrhea, and was used as an immunologic bridge between adults 18-45 years of age in the lot consistency trial (study 3), and older adults (study 4) and pediatric subjects (study 5).

Prespecified immunobridging analyses, based on differences in seroconversion rates, were performed to demonstrate non-inferiority. The seroconversion rates in vaccine and placebo recipients from each trial at 10 days post-vaccination, as well as immunobridging results, are summarised in Table 7 and Table 8 (14.3 Immunogenicity).

Study Results

Efficacy against cholera challenge

The efficacy of VAXCHORA vaccine in preventing moderate to severe diarrhea was demonstrated in adults ages 18-45 (study 2) showing that the vaccine protects against a live virulent *V. cholerae* O1 El Tor Inaba challenge at 10 days and 3 months post-vaccination (Table 6).

Table 6 - Study 2 Diarrheal Volume and Vaccine Efficacy in the Prevention of Moderate to Severe Diarrhea Following Challenge with *V. cholerae* O1 El Tor Inaba at 10 Days and 3 Months Post-Vaccination (Intent-to-Treat Population)

Parameter	VAXCHORA 10 day challenge[†] N=35	VAXCHORA 3 Month challenge[†] N=33	Combined, Placebo* 10 Day or 3 Month Challenge[†] N=66
Number of Subjects with Moderate or Severe Diarrhea (Attack Rate)[‡]	2 (5.7%)	4 (12.1%)	39 (59.1%)
Vaccine Efficacy %[§,¶] [95% CI]	90.3% [62.7%, 100.0%]	79.5% [49.9%, 100.0%]	
Diarrheal Volume (mL) GMV [95% CI] Min, Max	624.2 [147.2, 2645.9] 154, 18164	487.9 [237.3, 1003.5] 22, 9950	3495.1 [2651.3, 4607.4] 140, 24374

GMV=Geometric Mean Volume; CI=confidence interval; N=number of subjects challenged in each group.

* Combined placebo group comprised of all placebo recipients who were challenged at either 10 days (N=33) or 3 months (N=33) following vaccination.

† Challenge strain was *V. cholerae* O1 El Tor Inaba N16961.

‡ Moderate or severe diarrhea (≥ 3 liters of diarrhea) within 10 days after challenge.

§ Vaccine Efficacy=[(Attack Rate in Placebo Group – Attack Rate in Vaccine Group)/Attack Rate in Placebo Group] x 100.

¶ Pre-specified criteria for success were that the lower bound of the two-sided 95% confidence interval for vaccine efficacy must be ≥30% in both the 10 Day and 3 Month challenge groups.

In individuals with blood group O only, the protective efficacy against moderate or severe diarrhea was 84.8% in the 10-day challenge group (n=19) and 78.4% in the 3-month challenge group (n=20).

14.2 Comparative Bioavailability Studies

This information is not available for this drug product.

14.3 Immunogenicity

Adults 46 through 64 years were shown to have a non-inferior rate of seroconversion by classical Inaba vibriocidal antibody at 10 days post-vaccination compared to adults 18 through 45 years of age (Table 7).

Table 7 - Vibriocidal Antibody Seroconversion Against Classical Inaba *V. cholerae* Vaccine Strain at 10 Days Post-Vaccination in Adults

Study	VAXCHORA Recipients		Placebo Recipients		Difference in Seroconversion Rate Compared to Study 3 in 18-45 years old*
(age in years)	N	Seroconversion† % [95% CI]	N	Seroconversion† % [95% CI]	Percentage [95% CI]
Study 3 (18 – 45)	2687	93.5% [92.5%, 94.4%]	334	4.2% [2.3%, 6.9%]	-
Study 4 (46 – 64)	291	90.4% [86.4%, 93.5%]	99	0% [0.0%, 3.7%]	−3.1% [−6.7%, 0.4%]

CI=confidence interval; N= number of subjects with analyzable samples at Day 1 and Day 11.

* Non-inferiority criteria: lower bound of the two-sided 95% confidence interval on the difference in seroconversion rates compared with adults ages 18 to <46 years had to be greater than –10 percentage points and the lower bound of the two-sided 95% confidence interval on the proportion of vaccinees who seroconverted 10 days after vaccination had to be equal to or exceed 70%.

† Seroconversion is defined as the percentages of subjects who had at least a 4-fold rise in vibriocidal antibody titer at 10 days post-vaccination compared to baseline.

In study 2, serum vibriocidal seroconversion (4-fold increase) occurred in 79.8.% of all challenged and unchallenged vaccine recipients and 2% in placebo recipients 7 days post vaccination ($p<0.0001$). Vibriocidal seroconversion rates at 10 days post vaccination were 90.3% in challenged and unchallenged vaccine recipients and 2% in placebo recipients.

In the three adult studies increases in the percentage of anti-O1 lipopolysaccharide (LPS) IgA and IgG memory B cells and anti-cholera toxin IgG memory B cells were seen at 90 and 180 days after vaccination and increase in LPS IgA memory B cells was correlated with lower post cholera challenge stool volumes. Geometric mean titres (GMTs) of serum vibriocidal antibodies in vaccinated subjects were also higher than the respective GMTs of placebo recipients at 90 and 180 days after immunization in all age groups. The duration of protection is not known.

Children 2 through 17 years were shown to have a non-inferior rate of seroconversion by classical Inaba vibriocidal antibody at 10 days post-vaccination compared to adults 18 through 45 years of age. The pediatric seroconversion results in vaccine and placebo recipients and immunobridging results are shown in Table 8.

Table 8 - Vibriocidal Antibody Seroconversion Against Classical Inaba *V. cholerae* Vaccine Strain at 10 Days Post-Vaccination in Children aged 2 through 17 Years Compared to Adults 18 through 45 Years of Age

Study	VAXCHORA Recipients		Placebo Recipients		Difference in Seroconversion Rate Compared to Study 3 in 18-45 year old
(Age in years)	N	Seroconversion* % [95% CI]	N	Seroconversion* % [95% CI]	Percentage [95.0 % CI]†
Study 3 (18 – 45)	2687	93.5% [92.5%, 94.4%]	334	4.2% [2.3%, 6.9%]	-
Pediatric study 5 (2 – 17)	399	98.5% [96.8%, 99.3%]	67	1.5% [0.3%, 8.0%]	5.0% [3.0%, 6.3%]

CI=confidence interval; N= number of subjects with analyzable samples at Day 1 and Day 11 in the immunogenicity evaluable population.

* Seroconversion is defined as the percentages of subjects who had at least a 4-fold rise in vibriocidal antibody titer at 10 days post-vaccination compared to baseline.

† Non-inferiority criterion: lower bound of the two-sided 95.0 % confidence interval on the difference in seroconversion rate (study 5 minus study 3) must be greater than –10 percentage points.

A subset of participants (N=33) received <80% of the vaccine dose (see Table 9). In this subset, overall seroconversion was 75.8%. Seroconversion was 100% for subjects taking 50-80% of the dose (N=7) and 69.2% for subjects taking <50% of the dose (N=26).

Table 9 - Number of Subjects (%) with SVA Seroconversion at Day 10 Post Vaccination Stratified by Portion of Dose Consumed*

	<50% of Dose	≥50 to <80% of Dose	Total (<80% of Dose)
2 to 5 years	11/16 (68.8%)	6/6 (100%)	17/22 (77.3%)
6 to 11 years	6/9 (66.7%)	1/1 (100%)	7/10 (70.0%)
12 to 17 years	1/1 (100%)	0/0	1/1 (100%)
All age groups	18/26 (69.2%)	7/7 (100%)	25/33 (75.8%)

*Among Vaxchora subjects (modified intent-to-treat population) who consumed less than 80% of expected dose

Vibriocidal Antibody Against Classical Ogawa, El Tor Inaba and El Tor Ogawa

V. cholerae serogroup O1 consists of four major subtypes: classical Inaba, classical Ogawa, El Tor Inaba and El Tor Ogawa. Serum vibriocidal antibody against the three types of *V. cholerae* not contained in the vaccine, namely classical Ogawa, El Tor Inaba and El Tor Ogawa, was also measured in Study 2 and Study 4. The percentages of vaccine recipients who seroconverted against each of the 4 major

biotype/serotypes of *V. cholerae* serogroup O1 at 10 days post-vaccination (71.4% to 91.4%) are shown in Table 10.

Table 10 - Seroconversion Rates 10 Days Post-Vaccination for the Four Major *V. cholerae* O1 Serogroup Biotypes and Serotypes [Immunogenicity Evaluable Population]

Cholera Strain	Study 2 (18 – 45 years) VAXCHORA		Study 4 (46 – 64 years) VAXCHORA [a]	
	N	% [a] [95% CI]	N	% * [95% CI]
Classical Inaba†	93	90.3% [82.4%, 95.5%]	291	90.4% [86.4%, 93.5%]
El Tor Inaba	93	91.4% [83.8%, 96.2%]	290	91.0% [87.1%, 94.1%]
Classical Ogawa	93	87.1% [78.5%, 93.2%]	291	73.2% [67.7%, 78.2%]
El Tor Ogawa	93	89.2% [81.1%, 94.7%]	290	71.4% [65.8%, 76.5%]

N=number of subjects with measurements at baseline and 10 days post-vaccination. One subject in the younger adults study did not have a Day 11 measurement and was dropped from the analysis; CI=confidence interval.

* Seroconversion is defined as the percentages of subjects who had at least a 4-fold rise in vibriocidal antibody titer at 10 days post-vaccination compared to the titer measured at baseline.

† VAXCHORA vaccine contains the classical Inaba strain of *V. cholerae*

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether VAXCHORA vaccine affects fertility in males or females.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

VAXCHORA®

Cholera Vaccine, Live Attenuated, Oral

Read this carefully before you start taking **VAXCHORA** vaccine and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VAXCHORA** vaccine.

What is VAXCHORA vaccine used for?

- The vaccine is taken by mouth and is used to help protect people who are travelling to an area where there is a risk of diarrhea caused by cholera. It stimulates the body's natural defense in the gut and mimics the natural infection.
- The vaccine is used for protection from cholera in persons 2 to 64 years of age. The vaccine is effective against the most common serogroup of cholera (O1) but does not work against uncommon serogroups such as O139.

How does VAXCHORA vaccine work?

VAXCHORA vaccine prepares the immune system (the body's defenses) to fight against cholera bacteria if you come in contact with it. When you take the vaccine, the immune system makes proteins called antibodies against the cholera bacterium and its toxin (harmful substance) that causes diarrhea.

What are the ingredients in VAXCHORA vaccine?

Medicinal ingredients: live attenuated *V. cholerae* strain CVD 103-HgR.

Non-medicinal ingredients: ascorbic acid, hydrolysed casein, lactose, sodium bicarbonate, sodium carbonate and sucrose.

VAXCHORA vaccine comes in the following dosage forms:

VAXCHORA vaccine is a white-to-beige powder to be reconstituted into a suspension. Each dose of vaccine contains 4×10^8 to 2×10^9 colony forming units (CFU) of live attenuated *V. cholerae* strain CVD 103-HgR.

Do not use VAXCHORA vaccine if:

- You are allergic to any of the ingredients in the vaccine listed above.
- You had allergic reactions when you previously took a cholera vaccine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VAXCHORA vaccine. Talk about any health conditions or problems you may have, including if you:

- Have a weakened immune system, for example, if you were born with a weakened immune system or if you are having treatments such as high-dose corticosteroid treatment, cancer medicines or radiotherapy that can weaken the immune system.
- Have close contacts who have weakened immunity, as the bacteria from the vaccine may be present in your stool for at least 7 days after you take the vaccine. To prevent any

contamination, wash your hands thoroughly after visiting the toilet and before preparing food for at least 14 days after you take VAXCHORA vaccine.

Other warnings you should know about:

Do not give this vaccine to children younger than 2 years of age because it is not known how well it works in this age group.

Use of VAXCHORA vaccine in pregnant or breastfeeding women has not been studied. If you are considering taking VAXCHORA contact your healthcare professional.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with VAXCHORA vaccine:

- Antibiotics: The vaccine may not work if you take it while you are also taking antibiotics. Take VAXCHORA vaccine no earlier than 14 days after the last dose of an antibiotic, or do not take antibiotics for at least 10 days after taking VAXCHORA vaccine.
- Chloroquine for malaria prevention: VAXCHORA vaccine may not work if you take it while you are also taking chloroquine. Take the vaccine at least 10 days before starting chloroquine or 14 days after taking chloroquine.
- Oral Typhoid vaccine Ty21a: VAXCHORA vaccine may not work if it is taken at the same time as Ty21a. You should take it at least 2 hours before or after taking Ty21a.
- Food or drink: You must not eat or drink for one hour before or after taking VAXCHORA vaccine as this may reduce the vaccine's effectiveness.

How to take VAXCHORA vaccine:

Usual dose:

Always take this vaccine exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.

VAXCHORA vaccine is taken by mouth only.

The recommended dose is the contents of both sachets in the carton.

Protection against cholera is established within 10 days after taking VAXCHORA vaccine. Your healthcare professional will tell you how soon before travelling to take the vaccine.

Avoid eating or drinking one hour before and one hour after taking the vaccine**.**

Instructions:

PREPARE THIS VACCINE EXACTLY AS DESCRIBED IN THIS LEAFLET

Please read the following before you begin:

VAXCHORA vaccine may not work if the following occurs:

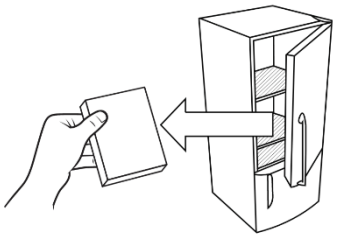
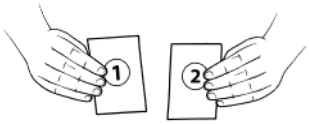
- Incorrect storage; the vaccine must be stored in the refrigerator.
- Using the incorrect amount of water; see step 4 below.

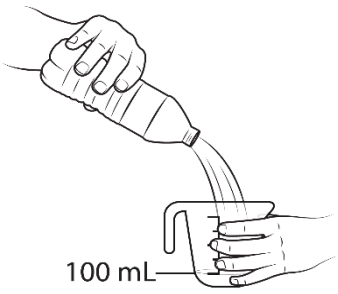
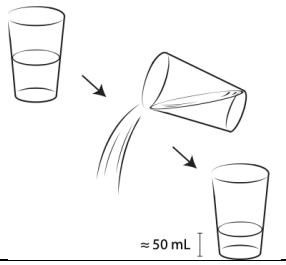
- Using the incorrect type of water; purified, spring or sparkling (carbonated) bottled water that is cold or room temperature must be used.
- Mixing the sachets in the wrong order; sachet 1 (**BUFFER**) must be added to the water first. If the sachets are mixed in the wrong order you must discard the vaccine and request a replacement dose.
- Eating or drinking; must be avoided one hour before and after taking the vaccine, eating or drinking can reduce the effectiveness of the vaccine.

Do not touch your eyes when you prepare the vaccine to avoid contamination.

If any powder or liquid gets spilled, clean the surface with hot water and soap or an antibacterial disinfectant.

If there is a significant spill (more than a few drops of liquid or grains of powder), dispose of the vaccine and get a new one from your doctor or pharmacist; DO NOT take the remaining medication.

Step 1	Gather materials: • Clean cup • Utensil to stir • Bottled water (purified, spring or sparking [carbonated]), cold or at room temperature, 25°C or less) • Item to measure 100 mL of bottled water (e.g. measuring cup) • Scissors
Step 2 	Remove the vaccine from the refrigerator.
Step 3 	Locate the two sachets: the sachets are labeled 1 and 2. Sachet 1 contains “BUFFER COMPONENT OF VAXCHORA” and is black and white. Sachet 2 contains “ACTIVE COMPONENT OF VAXCHORA” and is blue and white. If a sachet is not intact, do not use either sachet and contact your healthcare professional about acquiring a replacement dose; using a sachet that is not intact can reduce the effectiveness of the vaccine.

Step 4  	Measure 100 mL of cold or room temperature **bottled** water (purified, spring or sparkling [carbonated]) and pour into a clean cup. Do not use tap/faucet water, or any non purified bottled water, other beverages, or other liquids.
Step 5 	Use scissors to cut off the top of sachet 1. Do not put your fingers into the sachet.
Step 6 	Empty the contents of sachet 1 into the water in the cup. It will fizz.
Step 7 	Stir until the powder completely dissolves.
Step 8  	***For children age 2 to 5 years only:*** **Pour out and discard half of the buffer solution**

Step 9 	Use scissors to cut off the top of sachet 2. Do not put your fingers into the sachet. Wash your hands if you touch the sachet contents, in order to reduce the chance of contamination.
Step 10 	Empty the contents of sachet 2 into the cup.
Step 11 	Stir for at least 30 seconds. The powder from sachet 2 may not dissolve completely. It will form a slightly cloudy mixture with some white particles. If desired, no more than 4 gram (1 teaspoon) of table sugar or no more than 1 gram of stevia sweetener (1/4 teaspoon) may be added, and then stirred into the suspension.
Step 12 	If you have spilled any material, DO NOT take the remaining dose and contact your healthcare professional about acquiring a replacement dose. Drink the full contents of the cup within 15 minutes of preparing it. Some residue may remain in the cup and must be discarded.

Step 13 	Clean all used items with soap and hot water.
Step 14 	If a spill occurs while stirring or drinking the medication, or there is any residue (powder or liquid left behind from a stirring utensil, cup, or other object) on the mixing surface, clean up spilled material or residue, preferably with a disposable paper towel/cloth using hot water and soap or antibacterial disinfectant. Discard the paper towel together with the sachets (see below).
Step 15 	Discard sachets and any disposable items.
Step 16 	Wash your hands thoroughly with soap and hot water to prevent contamination.

Overdose:

If you take more than the recommended dose, you may have some of the side effects listed below.

If you think you, or a person you are caring for, have taken too much VAXCHORA vaccine, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Not applicable as there is only one dose of VAXCHORA vaccine.

Consumption of less than a half dose may result in decreased protection. If you consumed less than half the dose, contact your healthcare professional about acquiring a replacement dose. Consideration may be given to repeating a full dose of VAXCHORA vaccine within 72 hours.

Always make sure you take VAXCHORA vaccine a minimum of 10 days before potential exposure to cholera.

What are possible side effects from using VAXCHORA vaccine?

These are not all the possible side effects you may have when taking VAXCHORA vaccine. If you experience any side effects not listed here, tell your healthcare professional.

Contact a doctor immediately if you get the following serious side effects:

- serious allergic reactions causing swelling of the face or throat, hives, itchy rash, breathlessness and/or a drop in blood pressure and fainting.

The most common side effects of VAXCHORA vaccine were tiredness, headache, nausea/vomiting, abdominal pain and lack of appetite.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and Bavarian Nordic A/S cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit.

Also, to report an adverse event related to VAXCHORA® vaccine, please contact Bavarian Nordic A/S at 1-833-203-7933.

Storage:

Store VAXCHORA buffer component and active component sachets refrigerated at 2°C to 8°C. Protect

from light and moisture. Sachets should not be out of refrigerated storage for more than 12 hours prior to reconstitution; when out of refrigerated storage, sachets should not be exposed to temperatures above 25°C.

Keep out of reach and sight of children.

If you want more information about VAXCHORA vaccine:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website bnvaccines.ca, or contact medical.information_NA@bavarian-nordic.com or by calling 1-833-203-7933.

This leaflet was prepared by Bavarian Nordic A/S

Last Revised