

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Vaxchora effervescent powder and powder for oral suspension
Cholera vaccine (recombinant, live, oral)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of vaccine contains 4×10^8 to 2×10^9 viable cells of *V. cholerae* live, attenuated strain CVD 103-HgR¹.

¹ Produced by recombinant DNA technology.

This product contains genetically modified organisms (GMOs).

Excipient(s) with known effect: each dose of vaccine contains lactose, sucrose, and 863 milligrams of sodium.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent powder and powder for oral suspension.

White-to-off-white buffer powder and white-to-beige active ingredient powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vaxchora is indicated for active immunisation against disease caused by *Vibrio cholerae* serogroup O1 in adults and children aged 2 years and older.

This vaccine should be used in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Adults and children aged 2 years and older

A single oral dose should be administered at least 10 days prior to potential exposure to *V. cholerae* O1.

Revaccination

No data are available on revaccination interval.

Paediatric population

The safety and efficacy of Vaxchora in children less than 2 years has not been established. No data are available.

Method of administration

Oral use.

For instructions on reconstitution of Vaxchora prior to administration, see section 6.6.

Eating and drinking should be avoided for 60 minutes before and after oral ingestion of Vaxchora.

The reconstituted vaccine forms a slightly cloudy suspension that may contain some white particulates. After reconstitution, the suspension should be drunk within 15 minutes. The recipient should drink the full contents of the cup at once. Some residue may remain in the cup. The cup should be washed with soap and hot water.

Consumption of less than a half dose may result in decreased protection. If less than half the dose is consumed, consideration may be given to repeating a full dose of Vaxchora within 72 hours.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

Allergic reaction to previous ingestion of Vaxchora.

Individuals with congenital immune deficiency or receiving immunosuppressive drugs or treatments.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Factors affecting protection

Vaxchora confers protection specific to *Vibrio cholerae* serogroup O1. Immunisation does not protect against *V. cholerae* O139 or other species of *Vibrio*.

Vaxchora does not provide 100% protection. Vaccinees should adhere to hygiene advice and exercise caution regarding food and water consumed in cholera-affected areas.

No data are available in persons living in cholera-affected areas or in individuals with pre-existing immunity to cholera.

The protection afforded by Vaxchora may be reduced in HIV-infected individuals.

Potential risk to contacts

Vaxchora shedding in the stools was studied for 7 days post-vaccination, and was observed in 11.3% of vaccine recipients. The duration of shedding of the vaccine strain is unknown. There is a potential for transmission of the vaccine strain to non-vaccinated close contacts (e.g., household contacts).

Concomitant administration with antibacterial agents and/or chloroquine

Concomitant administration with antibacterial agents and/or chloroquine should be avoided because protection against cholera may be diminished. Refer to section 4.5.

Gastrointestinal Disease

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.

Limitations of the clinical data

Clinical trials were conducted in individuals age 2 to 64 years old. Efficacy was demonstrated using human cholera challenge at 10 days or 3 months post-vaccination in adults age 18-45 years and immunobridging to other populations based on seroconversion rate. Immunogenicity data are available for 24 months post-vaccination (see section 5.1). There are no immunogenicity or efficacy data in individuals over 64 years of age.

Excipients

The vaccine contains lactose and sucrose. Patients with rare hereditary problems of galactose intolerance, congenital lactase deficiency, glucose-galactose malabsorption, fructose intolerance, or sucrose-isomaltase insufficiency should not take this vaccine.

The vaccine contains 863 mg of sodium per dose, equivalent to 43% of the WHO recommended maximum daily intake of 2 g of sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Vaxchora, however data and clinical experience from other vaccines can be applicable to Vaxchora.

There should be an interval of 2 hours between the administration of Vaxchora and of typhoid vaccine Ty21a (gastro-resistant capsules) as the buffer administered with Vaxchora may affect the transit of the capsules through the gastrointestinal tract.

Concomitant administration of Vaxchora with systemic antibiotics active against *V. cholerae* should be avoided since these agents may prevent a sufficient degree of multiplication to occur in order to induce a protective immune response. Vaxchora should not be administered 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.

Data from the study of a previous CVD 103-HgR-based vaccine indicate that immune responses to Vaxchora and protection against cholera may be diminished when Vaxchora is administered concomitantly with chloroquine. Administer Vaxchora at least 10 days before beginning antimalarial prophylaxis with chloroquine. There are no data regarding concomitant use of Vaxchora with other anti-malarial drugs.

The vaccine is acid-labile and is administered with a buffer. Eating and drinking should be avoided for 60 minutes before and after taking Vaxchora as this may interfere with the protective effect of the buffer.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of Vaxchora in pregnant women.

Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Vaxchora should be used during pregnancy only if the potential benefits to the mother outweigh the potential risks, including those to the foetus.

Breast-feeding

It is unknown whether Vaxchora is excreted in human milk. A risk to the breastfed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to abstain from using Vaxchora taking into account the benefit of breast feeding for the child and the benefit of Vaxchora for the woman.

Fertility

No human or animal data on the effect of Vaxchora on fertility are available.

4.7 Effects on ability to drive and use machines

Vaxchora has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

The most frequent reported adverse reactions following Vaxchora administration are tiredness (30.2%), headache (28.3%), abdominal pain (18.4%), nausea/vomiting (17.7%), and lack of appetite (15.7%).

Tabulated summary of adverse reactions

The adverse reaction frequency classification used is as follows: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Adverse Reactions	Frequency
<i>Metabolism and nutrition disorders</i>	
Decreased appetite	Very common
<i>Nervous system disorders</i>	
Headache	Very common
Dizziness	Uncommon
<i>Gastrointestinal disorders</i>	
Abdominal pain, nausea/vomiting	Very common
Diarrhoea	Common
Flatulence, constipation, abdominal distension, dyspepsia, abnormal faeces, dry mouth, eructation	Uncommon
<i>Skin and subcutaneous tissue disorders</i>	
Rash	Uncommon
<i>Musculoskeletal and connective tissue disorders</i>	
Arthralgia	Uncommon
Chills	Rare
<i>General disorders and administration site conditions</i>	
Fatigue	Very common
Pyrexia	Uncommon

Paediatric population

A clinical trial was conducted in 550 children age 2 to <18 years. Based on the results of this trial the type of adverse reactions in children are expected to be similar to those in adults. Some adverse reactions were more common in children than adults, including fatigue (35.7% vs 30.2%), abdominal pain (27.8% vs 18.4%), vomiting (3.8% vs 0.2%), decreased appetite (21.4% vs 15.7%) and pyrexia (2.4% vs 0.8%).

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 Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bacterial vaccines, ATC code: J07AE02

Mechanism of action

Vaxchora contains live attenuated cholera bacteria (*V. cholerae* O1 classical Inaba strain CVD 103-HgR) that replicate in the gastrointestinal tract of the recipient and induce serum vibriocidal antibody and memory B cell responses. Immune mechanisms conferring protection against cholera following receipt of Vaxchora have not been determined, however, rises in serum vibriocidal antibody 10 days after vaccination with Vaxchora were associated with protection in a human challenge study.

Efficacy against cholera challenge

Vaxchora efficacy against cholera was demonstrated in a human challenge study conducted in 197 healthy adult volunteers mean age 31 years (range 18 to 45, 62.9% male, 37.1% female) in which a subset of Vaxchora or placebo recipients were challenged with live *V. cholerae* at 10 days post-vaccination (n=68) or 3 months post-vaccination (n=66). Protective efficacy against moderate to severe diarrhoea is shown in Table 1.

In individuals with blood group O only, the protective efficacy against moderate or severe diarrhoea was 78.4% in the 10 day challenge group (n=19) and 82.5% in the 3 month challenge group (n=20).

Table 1: Protective Efficacy in the Prevention of Moderate to Severe Diarrhoea 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 Diarrhoea (Attack Rate)	2 (5.7%)	4 (12.1%)	39 (59.1%)
Protective Efficacy % [95% CI]	90.3% [62.7%, 100.0%]	79.5% [49.9%, 100.0%]	-

Immunogenicity

The human challenge study showed that vibriocidal seroconversion, defined as a four-fold or greater rise in serum vibriocidal antibody titres from baseline measured 10 days after vaccination, had a nearly one-to-one correlation with protection against moderate-to-severe diarrhoea. Seroconversion was therefore selected as the immunologic bridge between adults age 18 to <46 years in the challenge study and other populations, i.e. older adults and paediatric subjects. Three additional studies evaluated immunogenicity: a large trial in 3146 healthy adults age 18 to <46 years (mean age 29.9, range 18-46, 45.2% male, 54.8% female); a trial in 398 healthy older adults age 46 to <65 years (mean age 53.8, range 46-64, 45.7% male, 54.3% female); and a paediatric trial in healthy subjects age 2-<18 years. Prespecified immunobridging analyses, based on differences in seroconversion rates, were determined to demonstrate non-inferiority in seroconversion rate between older adults or paediatric subjects and the adults age 18 to <46 in the large immunogenicity trial.

The seroconversion rates in vaccine and placebo recipients from each trial at 10 days post-vaccination, as well as immunobridging results, are summarised in Tables 2 and 4. In the challenge study, 79.8% of subjects seroconverted by 7 days post-vaccination. Seroconversion rates in older adults and paediatric subjects were non-inferior to those in younger adults.

In the three 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. No relationship between age and memory B cell response was observed. Geometric mean titres (GMTs) of serum vibriocidal antibodies in vaccinated subjects were also significantly higher than the respective GMTs of placebo recipients at 90 and 180 days after immunisation in all age groups. The duration of protection is not known.

Table 2: Vibriocidal Antibody Seroconversion Against Classical Inaba *V. cholerae* Vaccine Strain at 10 Days Post-Vaccination in Adults

Study (age in years)	Vaxchora Recipients		Placebo Recipients		Immunobridging: Difference in Seroconversion Rate Compared to Large Trial in 18- 45 year olds
	N ^b	Seroconversion ^a % [95% CI]	N ^b	Seroconversion ^a % [95% CI] ^c	% ^d [95% CI] ^c
Challenge Trial (18 – 45)	93	90.3% [82.4%, 95.5%]	102	2.0% [0.2%, 6.9%]	-
Large Trial (18 – 45)	2687	93.5% [92.5%, 94.4%]	334	4.2% [2.3%, 6.9%]	-
Older Adults (46 – 64)	291	90.4% [86.4%, 93.5%]	99	0% [0.0%, 3.7%]	-3.1% [-6.7%, 0.4%]

^a 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.

^b N=number of subjects with analyzable samples at Day 1 and Day 11.

^c CI=confidence interval.

^d Non-inferiority criteria: lower bound of the two-sided 95% confidence interval on the difference in seroconversion rates compared with adults age 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%.

Available data on seroconversion rates against other biotypes and serotypes of *V. cholerae* are shown in Table 3. Seroconversion rates for these biotypes and serotypes were not determined in children.

Table 3: Seroconversion Rates 10 Days Post-Vaccination for the Four Major *V. cholerae* O1 Serogroup Biotypes and Serotypes [Immunogenicity Evaluable Population]

Cholera Strain	Younger Adults (18 through 45 year olds)		Older Adults (46 through 64 year olds)	
	N ^a	Vaxchora % ^b [95% CI] ^c	N ^a	Vaxchora % [95% CI]
Classical Inaba ^d	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%]

^a 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.

^b 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.

^c CI=confidence interval.

^d Vaxchora contains the classical Inaba strain of *V. cholerae* O1.

Paediatric population

An immunogenicity trial was conducted in 550 healthy children age 2 to <18 years (mean age 9.0, range 2-17, 52.0% male, 48.0% female). In the immunogenicity evaluable population (n=446) the ratio of male to female was 52.8% male and 47.2% female. The seroconversion results in vaccine and placebo recipients and immunobridging results are shown in Table 4.

Long-term immunogenicity data are available from a subset of children age 12 to <18 years. The seroconversion rate ranged from 100% at 28 days post-vaccination to 64.5% at 729 days post-vaccination. The seroconversion results over time are shown in Table 5.

Table 4: Vibriocidal Antibody Seroconversion Against Classical Inaba *V. cholerae* Vaccine Strain at 10 Days Post-Vaccination in Children [Immunogenicity Evaluable Population]

Study (age in years)	Vaxchora Recipients		Placebo Recipients		Immunobridging : Difference in Seroconversion Rate Compared to Large Trial in 18-45 year olds
	N ^b	Seroconversion ^a % [98.3% CI]	N ^b	Seroconversion ^a n ^a % [95% CI ^c]	
Paediatric Trial (2 – <18)	399	98.5% [96.2%, 99.4%]	67	1.5% [0.3%, 8.0%]	5.0% [2.8%, 6.4%] ^c

^a 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.

^b N=number of subjects with analyzable samples at Day 1 and Day 11.

^c CI=confidence interval.

^d Non-inferiority criteria: lower bound of the two-sided 98.3% 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 98.3% confidence interval on the proportion of vaccinees who seroconverted 10 days after vaccination had to be equal to or exceed 70%.

Table 5: Vibriocidal Antibody Seroconversion Against Classical Inaba *V. cholerae* Vaccine Strain 10 through 729 Days Post-Vaccination in Children age 12 to <18 Years [Immunogenicity Evaluable Population in the Long-Term Follow-up Substudy]

Paediatric Trial (12 - < 18 years) Day Post-Vaccination	VAXCHORA N^b	VAXCHORA Seroconversion^a % [95% CI^c]
10	72	100.0% [94.9%, 100.0%]
28	72	100.0% [94.9%, 100.0%]
90	72	88.9% [79.6%, 94.3%]
180	71	83.1% [72.7%, 90.1%]
364	70	68.6% [57.0%, 78.2%]
546	67	73.1% [61.5%, 82.3%]
729	62	64.5% [52.1%, 75.3%]

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

^b N=number of subjects with analyzable samples in the immunogenicity evaluable population of the long term follow-up sub-study.

^c CI=confidence interval.

The European Medicines Agency has deferred the obligation to submit the results of studies with Vaxchora in one or more subsets of the paediatric population in the prevention of cholera (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

No preclinical safety data are available for Vaxchora.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Buffer, sachet 1:

Sodium bicarbonate

Sodium carbonate

Ascorbic acid

Lactose

Active ingredient, sachet 2:

Sucrose

Hydrolysed casein

Ascorbic acid

Lactose

6.2 Incompatibilities

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

6.3 Shelf life

18 months.

Vaxchora stored in the outer carton is stable at 25°C for up to 12 hours.

After reconstitution (see section 6.6), the suspension should be drunk within 15 minutes.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Store in the original package.

Avoid exposure to temperatures above 25°C.

6.5 Nature and contents of container

Carton box containing one active ingredient sachet and one buffer sachet.

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

The buffer sachet 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 aluminium 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 aluminium foil and an inner layer of low-density polyethylene.

Pack size: 1 set of 2 sachets.

6.6 Special precautions for disposal

This medicinal product contains genetically modified organisms. Unused medicinal product must be disposed of in compliance with the local biosafety guidelines.

To prepare the vaccine for administration the Vaxchora active and buffer component sachets are removed from the refrigerator no more than 12 hours at 25°C prior to reconstitution.

It is important to mix the sachets in the order described. First, the contents of the buffer sachet 1 (a white-to-off-white powder) are mixed with 100 mL of cold or room temperature ($\leq 25^{\circ}\text{C}$) bottled non-carbonated drinking water in a cup. For children age 2 to <6 years ONLY, half (50 mL) of the buffer solution should then be discarded before proceeding to the next step. Second, the contents of the active component sachet 2 (a white-to-beige powder) are then added and the mixture is stirred for at least 30 seconds. The reconstituted vaccine forms a slightly cloudy suspension that may contain some white particulates. Sucrose (up to 4 g/ 1 teaspoon) or stevia sweetener (no more than 1 gram / $\frac{1}{4}$ teaspoon) may then be stirred into the suspension if desired. DO NOT add other sweeteners as this may reduce the effectiveness of the vaccine. The dose should be administered within 15 minutes of reconstitution.

Note: if the sachets are reconstituted in the incorrect order, the vaccine must be discarded.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PLGB 43552/0006

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

01 April 2020

10 DATE OF REVISION OF THE TEXT

08 September 2021