ANNEX I

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 x 10^8 to 2 x 10^9 viable cells of *V. cholerae* live, attenuated strain CVD 103-HgR[1].
[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 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 administrated 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 in a human cholera challenge at 10 days or 3 months post-vaccination in adults age 18-45 years and immunobridging to other populations based on the rate of seroconversion. 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 a healthy 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 replication 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 (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Adverse Reactions	**Frequency**
Metabolism and nutrition disorders	
Decreased appetite	Very common
Nervous system disorders	
Headache	Very common
Dizziness	Uncommon
Gastrointestinal disorders	
Abdominal pain, nausea/vomiting	Very common
Diarrhoea	Common
Flatulence, constipation, abdominal distension, dyspepsia, abnormal faeces, dry mouth, eructation	Uncommon
Skin and subcutaneous tissue disorders	
Rash	Uncommon
Musculoskeletal and connective tissue disorders	
Arthralgia	Uncommon
Chills	Rare
General disorders and administration site conditions	
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 national reporting system listed in Appendix V.

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 10day 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	**Vaxchora Recipients**		**Placebo Recipients**		**Immunobridging: Difference in Seroconversion Rate Compared to Large Trial in 18-45 year olds**
		Seroconversion[a] %		Seroconversion[a] %	%[d]
(age in years)	N[b]	[95% CI]	N[b]	[95% CI[c]]	[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]

	Younger Adults (18 through 45 year olds) Vaxchora		Older Adults (46 through 64 year olds) Vaxchora	
Cholera Strain	N[a]	%[b] [95% CI[c]]	N[a]	% [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=466) 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	**Vaxchora Recipients**		**Placebo Recipients**		**Immunobridging: Difference in Seroconversion Rate Compared to Large Trial in 18-45 year olds**
		Seroconversion[a] %		Seroconversion[a] %	%[d]
(age in years)	N[b]	[98.3% CI]	N[b]	[95% CI[c]]	[96.7% CI]
Paediatric Trial (2 – <18)	399	98.5% [96.2%, 99.4%]	67	1.5% [0.3%, 8.0%]	5.0% [2.8%, 6.4%][e]

[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 of used medicinal product or waste materials and other handling of the product

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 (≤25°C) non-carbonated or carbonated bottled 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 / ¼ 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

Bavarian Nordic A/S
Philip Heymans Alle 3

DK-2900 Hellerup
Denmark

8. MARKETING AUTHORISATION NUMBER

EU/1/20/1423/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 2020

10. DATE OF REVISION OF THE TEXT

{DD month YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Bavarian Nordic Berna GmbH
Oberriedstrasse 68
CH-3174 Thörishaus
Switzerland

Name and address of the manufacturer(s) responsible for batch release

IL-CSM GmbH
Marie-Curie-Strasse 8
D-79539 Lörrach
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile

or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Vaxchora in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.
The educational programme is aimed at minimising the risk of medication errors during the reconstitution and use of the product.
The MAH shall ensure that in each Member State where Vaxchora is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Vaxchora have access to/are provided with the following educational package:

- Health care professional educational material
- Patient information pack

Health care professional educational material:

- The Summary of Product Characteristics
- Guide for healthcare professionals
- Patient Guide

Guide for healthcare professionals key messages:

- That there is an important potential risk of medication errors during the reconstitution and use of Vaxchora,
- There is an increased potential risk of medication errors when the vaccine is prepared and given to children 2 to < 6 years old
- The patients/caretakers should be informed about and follow the reconstitution instructions as advised
- The healthcare professionals should council the patients and their caretakers on how to reconstitute and administer Vaxchora
- Detailed description of the administration procedures of Vaxchora

The patient information pack:

- Patient information leaflet
- A patient/carer guide

Patient/carer guide key messages:

- That it is important that Vaxchora is reconstituted and administered as instructed
- Increased attention to instructions should be given when preparing and administering vaccine to children 2 to < 6 years of age
- Detailed description of the modalities used for the self-administration of Vaxchora
- The importance of reporting medication errors.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Single carton box

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

$4x10^8$ to $2x10^9$ viable cells of *V. cholerae* strain CVD 103-HgR.

3. LIST OF EXCIPIENTS

Contains sucrose, lactose, and sodium. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 sachet powder for oral suspension
1 sachet effervescent powder
One dose.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Mix the effervescent powder (sachet 1) with bottled water (for children 2 to <6 years ONLY, discard half the solution) then add the active ingredient (sachet 2) and mix prior to taking.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bavarian Nordic A/S
Philip Heymans Alle 3
DK-2900 Hellerup
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1423/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vaxchora

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Sachet

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Vaxchora active ingredient
powder for oral suspension
cholera vaccine strain
Oral use

2. METHOD OF ADMINISTRATION

To be used with effervescent powder dissolved in bottled water.
Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.0 g

6. OTHER

2

Please see other side for instructions.

Sachet 2 of 2. Use last.

Bavarian Nordic A/S

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Sachet

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Sodium hydrogen carbonate effervescent powder
Oral use

2. METHOD OF ADMINISTRATION

To be mixed with bottled water and Vaxchora active ingredient.
Read the package leaflet before use especially if using in Children aged 2 to <6 years as different preparation steps are required.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

4.5 g

6. OTHER

1

Please see other side for instructions.

Sachet 1 of 2. Use first.

Bavarian Nordic A/S

B. PACKAGE LEAFLET

Package leaflet: Information for the user

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

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you take this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This vaccine has been prescribed for you only. Do not pass it on to others.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vaxchora is and what it is used for

Vaxchora is an oral vaccine against cholera that stimulates the immunological defence in the gut. The vaccine is used for protection from cholera in adults and children aged 2 years and older. The vaccine must be taken at least 10 days before travelling to a cholera-affected area.

How Vaxchora works

Vaxchora prepares the immune system (the body's defences) to defend itself against cholera. When a person takes the vaccine, the immune system makes proteins called antibodies against the cholera bacterium and its toxin (harmful substance) that causes diarrhoea. In this way the immune system is ready to fight cholera bacteria if the person comes into contact with it.

2. What you need to know before you take Vaxchora

Do not take Vaxchora:
- if you are allergic to any of the ingredients in this medicine (listed in section 6).
- if you had allergic reactions when you previously took Vaxchora.
- 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.

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before taking Vaxchora.

Not everyone taking Vaxchora will be fully protected against cholera. It is important to continue to follow hygiene advice and take special care with food and water in cholera-affected areas.

Vaxchora may be less effective if you have HIV.

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, changing nappies and before preparing food for at least 14 days after you take Vaxchora.

Children and adolescents
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.

Other medicines and Vaxchora
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines or vaccines. This includes medicines obtained without a prescription, including herbal medicines. This is because Vaxchora can affect the way some other medicines and vaccines work.

In particular tell your doctor, pharmacist or nurse if you are taking:
- antibiotics – Vaxchora may not work if you take it while you are also taking antibiotics. Take Vaxchora no earlier than 14 days after the last dose of an antibiotic. Avoid antibiotics for 10 days after taking Vaxchora.
- chloroquine for malaria prevention – Vaxchora may not work if you take it while you are also taking chloroquine. Take Vaxchora at least 10 days before starting chloroquine or 14 days after taking chloroquine.
- the typhoid vaccine Ty21a – Vaxchora may not work if it is taken at the same time as Ty21a. You should take Vaxchora at least 2 hours before or after taking Ty21a.

If any of the above apply to you, talk to your doctor, pharmacist or nurse before taking Vaxchora.

Vaxchora with food and drink
You must not eat or drink for 60 minutes before and after taking Vaxchora as this may reduce the vaccine's effectiveness.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Vaxchora is not likely to affect your ability to drive or use machines. However, do not drive or use any machines if you are feeling unwell.

Vaxchora contains lactose, sucrose, and sodium
If you have been told by your doctor that you have an intolerance to some sugars contact your doctor before taking this medicinal product.

This vaccine contains 863 mg of sodium (the main component of cooking/table salt) per dose. This is equivalent to 43% of the recommended daily dietary intake of sodium for an adult. Please take this into account if you are on a controlled sodium diet.

3. How to take Vaxchora

Always take this vaccine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

The recommended dose is the contents of both sachets in the carton. However for children 2 to less than 6 years old take note of Step 8 in the instructions on how to prepare the vaccine, shown below.

Protection against cholera is established within 10 days after taking Vaxchora. Your doctor, pharmacist or nurse will tell you how soon before travelling to take the vaccine.

Instructions:

PREPARE THIS VACCINE EXACTLY AS DESCRIBED IN THIS LEAFLET

Please read the following before you begin:

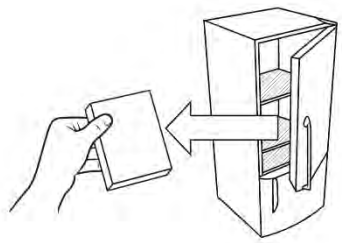
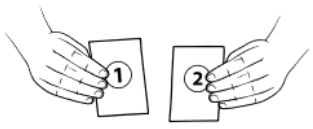
Vaxchora may not work if the following occurs:

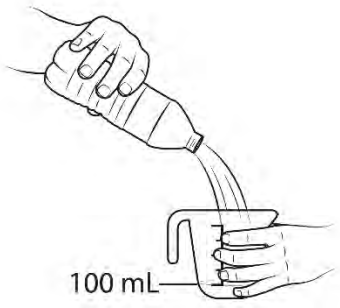
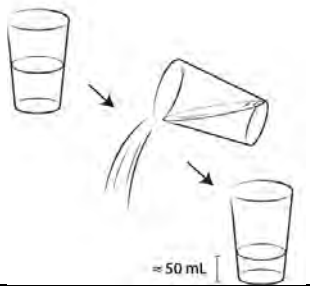
- Incorrect storage; the vaccine must be stored in the refrigerator.
- Using the incorrect amount of water; 100 mL must be used.
- Using the incorrect type of water; bottled water that is cold or room temperature and non-carbonated or carbonated must be used.
- Mixing the sachets in the wrong order; sachet 1 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 60 minutes 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 spilt, 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 (non-carbonated or carbonated, cold or room temperature, 25°C or less) • Item to measure 100 mL of bottled water (e.g. measuring jug) • Scissors
Step 2 	Remove the vaccine from the refrigerator.
Step 3 	Locate the two sachets: the sachets are labelled 1 and 2. Sachet 1 contains “Sodium hydrogen carbonate effervescent powder” (buffer) and is black and white. Sachet 2 contains “Vaxchora® Active ingredient” and is blue and white. If a sachet is not intact, do not use either sachet and contact your doctor, pharmacist or nurse 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 **bottled** cold or room temperature non-carbonated or carbonated water and pour into a clean cup. Using bottled water is necessary for the vaccine to be effective –using non-bottled (e.g. tap water) may render the vaccine ineffective.
Step 5		Use scissors to cut off the top of sachet 1. 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 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 <6 years only:*** Pour away and discard half of the buffer solution. (Note: For children over 6 years and adults this step is NOT required)
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, after stirring in sachet 2 for at least 30 seconds, stevia sweetener (no more than 1 gram or ¼ teaspoon) or sugar (sucrose, not more than 4 grams or 1 teaspoon) may be added, and then stirred into the suspension. DO NOT add other sweeteners as this may reduce the effectiveness of the vaccine.
Step 12		Drink the full contents of the cup within 15 minutes of preparing it. Some residue may remain in the cup and must be discarded. If you or your child take less than half of the dose, contact your doctor, pharmacist, or nurse right away about the need for a repeat dose.
Step 13		Dispose of the empty sachets according to local biosafety guidelines. Ask your doctor, pharmacist or nurse how to throw away medicine waste material.
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 above).
Step 15		Wash the cup and spoon or stirrer with soap and hot water.

Step 16		Wash your hands thoroughly with soap and hot water to prevent contamination.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

Like all vaccines, this vaccine can cause side effects, although not everybody gets them.

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.

Other side effects:
Very common side effects (may affect more than 1 in 10 people)

- headache,
- stomach pains,
- feeling or being sick,
- lack of appetite,
- tiredness.

Common side effects (may affect up to 1 in 10 people)

- diarrhoea.

Uncommon side effects (may affect up to 1 in 100 people)

- flatulence,
- constipation,
- bloating (abdominal distension),
- indigestion,
- abnormal faeces,
- dry mouth,
- burping,
- fever,
- dizziness,
- joint pain,
- rash.

Rare side effects (may affect up to 1 in 1,000 people):

- chills.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Vaxchora

Keep this vaccine out of the sight and reach of children.

Do not use Vaxchora after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).
Store in the original package.
Vaxchora in the original package is stable for up to 12 hours at 25°C. Avoid exposing Vaxchora to temperatures above 25°C.

Do not use this vaccine if you notice the sachets are damaged and contact your doctor, pharmacist, or nurse for a replacement dose.

This medicine contains genetically-modified organisms. Local biosafety guidelines should be followed for unused medicine or waste material. Ask your doctor, pharmacist or nurse how to throw away medicines you no longer use or waste material.

6. Contents of the pack and other information

What Vaxchora contains
- Each dose contains $4x10^8$ to $2x10^9$ viable cells of *V. cholerae* strain CVD 103-HgR.
- The other ingredients are sucrose, hydrolysed casein, ascorbic acid, lactose, sodium bicarbonate, and sodium carbonate.
- This vaccine contains genetically modified organisms (GMOs).

What Vaxchora looks like and contents of the pack
The carton contains two sachets. One sachet contains white-to-off-white buffer sodium hydrogen carbonate effervescent powder. The other sachet contains white-to-beige active ingredient vaccine powder.

Marketing Authorisation Holder

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Manufacturer

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This leaflet was last revised in MM/YYYY.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.