Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

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Subject: Safety and Utilization Review for the Pediatric Advisory Committee

Applicant: Bavarian Nordic A/S

Product: VAXCHORA (Cholera Vaccine, Live, Oral)

STN: 125597/242

Indication: VAXCHORA is a vaccine indicated for active immunization against disease caused by *Vibrio cholerae* serogroup O1 in persons 2 through 64 years of age traveling to cholera-affected areas.

1.1 Limitations of Use
The effectiveness of VAXCHORA has not been established in persons living in cholera-affected areas.

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

VAXCHORA has not been shown to protect against disease caused by *V. cholerae* serogroup O139 or other non-O1 serogroups.

Meeting Date: Pediatric Advisory Committee Meeting, November 13, 2025

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1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review was the approval of the supplemental Biologics License Application (sBLA) 125597/123 on December 23, 2020, for use of Vaxchora in individuals 2 years to <18 years of age traveling to cholera-affected areas.

This memorandum documents the Food and Drug Administration's (FDA's) complete evaluation, including review of adverse event (AE) reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Indication and Product Description

VAXCHORA is a vaccine indicated for active immunization against disease caused by *Vibrio cholerae* serogroup O1. VAXCHORA is approved for use in persons 2 through 64 years of age traveling to cholera-affected areas. The following Limitations of Use are included:

> *The effectiveness of VAXCHORA has not been established in persons living in cholera-affected areas.*
>
> *The effectiveness of VAXCHORA has not been established in persons who have pre-existing immunity due to previous exposure to V. cholerae or receipt of a cholera vaccine.*
>
> *VAXCHORA has not been shown to protect against disease caused by V. cholerae serogroup O139 or other non-O1 serogroups.*

VAXCHORA is a suspension for oral administration only. It should be prepared and administered in a healthcare setting equipped to dispose of medical waste. Before reconstitution, each dose of VAXCHORA is supplied as a foil packet of buffer and an accompanying foil packet of the active component (lyophilized *V. cholerae* CVD 103-HgR). After reconstitution, a single dose of VAXCHORA is 100 mL (50 mL for children 2 through 5 years of age). Vaxchora is administered as a single dose a minimum of 10 days before potential exposure to cholera.

1.3 Regulatory History

- June 10, 2016: Initial approval of BLA 125597/0 for use in individuals 18 through 64 years of age traveling to cholera-affected areas
- December 23, 2020: Approval of sBLA 125597/123 to expand the usage to include children 2 to < 18 years of age traveling to cholera-affected areas upon fulfillment of

the Pediatric Research Equity Act (PREA) postmarketing requirement (PMR # 1 identified in the June 10, 2016, approval letter for BLA STN 125597/0) which serves as the trigger for this PAC (please see section 5.2 of memorandum).:

2 MATERIALS REVIEWED

- Vaccine Adverse Events Reporting System (VAERS)
    - VAERS reports for Vaxchora during December 23, 2020, to June 30, 2025 (safety review period)
- Manufacturer's Submissions
    - Vaxchora U.S. prescribing information; updated February 2025
    - Applicant response to information request regarding dose distribution data, received August 11, 2025
    - Pharmacovigilance Plan, Version 4.0, dated September 3, 2020
    - Periodic safety reports
- FDA Documents
    - BL 125597/123 sBLA approval letter dated December 23, 2020
    - BL 12597/0 BLA approval letter dated June 10, 2016
- Publications (see Literature Search in Section 7)

3 SAFETY-RELATED LABEL CHANGES IN REVIEW PERIOD

There were no safety related labeling changes during the PAC review period December 23, 2020, to June 30, 2025.

4 PRODUCT UTILIZATION DATA

Bavarian Nordic provided estimates of Vaxchora distribution data for the U.S. and worldwide for the safety review period (December 23, 2020, to June 30, 2025):

- U.S doses distributed
- Worldwide doses distributed

As noted previously, Vaxchora is administered as a single dose vaccine. The sponsor was not able to provide data on the proportion of doses distributed to pediatric (<18 years) and adult patients (18 years and older). Note that the number of doses distributed is an estimate of the number of individuals vaccinated.

These estimates were provided by the manufacturer for FDA review. Distribution data is protected as confidential commercial information and may require redaction from this review.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's current Pharmacovigilance Plan (PVP), Version 4.0, dated September 3, 2020, lists the following important identified risks, potential risks, and missing information for Vaxchora (see Table 1).

Table 1: Vaxchora Safety Concerns

Important Identified Risks
Hypersensitivity to any of the components of vaccine or buffer
Potential for shedding and subsequent transmission
Lack of protection against non-O1 cholera serogroup
Lack of 100% protection against *V. cholerae* O1
Reduction in efficacy when stored above the recommended temperature, or when administered >30 minutes after reconstitution
Important Potential Risks
Reduced immune response/decreased vaccine effectiveness when used concomitantly with antibiotics
Reduced immune response/decreased vaccine effectiveness when used in immunocompromised patients or along with immunosuppressive therapies
Exacerbation of existing gastrointestinal or febrile illness.
Missing Information
Use in adults aged 65 years or older
Use during pregnancy

Most of the important identified and potential risks listed in Table 1 are labeled events. Vaxchora is contraindicated in persons who have a history of severe allergic reaction (e.g., anaphylaxis) to any ingredient of Vaxchora or to a previous dose of any cholera vaccine. Shedding and transmission are included under Warnings and Precautions of the USPI. Vaxchora may be shed in the stool of recipients for at least 7 days. There is a potential for transmission of the vaccine strain to non-vaccinated close contacts (e.g., household contacts). USPI, Section 1.1 *Limitations of Use* states that, Vaxchora has not been shown to protect against disease caused by *V. cholerae* serogroup O139 or other non-O1 serogroups. Vaccine efficacy data is included under USPI section 14 *Clinical Studies*. USPI *Section 16.2 Storage and Handling* provides information on refrigeration of Vaxchora buffer and active components. USPI Section 2.3 Preparation, *Reconstitution and Administration* instructs individuals to consume Vaxchora within 30 minutes, if sucrose or non-flavored stevia are added. USPI Section 7 *Drug Interactions – Concomitant Vaccines or Medications* describes interaction with antibiotics. The safety and effectiveness of Vaxchora have not been established in immunocompromised persons, stated under *Warnings and Precautions* of USPI.

The important and potential risks for Vaxchora are monitored with routine safety surveillance, including review of adverse events reports submitted to the FDA, manufacturer submitted periodic safety reports, published literature and data mining. There are no postmarketing requirement/commitment (PMR/PMC) safety-related

studies or Risk Evaluation and Mitigation Strategy (REMS) for Vaxchora. Please see section 5.2 for a discussion of completed postmarketing studies.

5.2 Postmarketing Studies

The initial approval of Vaxchora included the following PMR under PREA:

- Deferred pediatric study (PXVX-VC-200-006) under PREA for active immunization against disease caused by *V. cholerae* serogroup O1 in pediatric patients ages 2 years to less than 18 years traveling to cholera-affected areas. This study will evaluate the safety and immunogenicity of VAXCHORA in this age group.

Study status: Study completed and PREA PMR was fulfilled with December 23, 2020, approval of sBLA 125597/123 which serves as the trigger for this review for the PAC (see sections 1.1 and 1.3 of this memorandum). No new safety concerns were identified from this study.

6 ADVERSE EVENT REVIEW

6.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of Vaxchora between December 23, 2020, to June 30, 2025. VAERS stores postmarketing adverse events and medication errors submitted to FDA and CDC for all approved vaccines. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a vaccine. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the vaccine.

6.2 Results

The results of the VAERS search of AE reports for Vaxchora during the safety review period are listed in Table 2 below. There were 48 reports, including 39 U.S. and 9 foreign reports, received during the review period December 23, 3020 to June 30, 2025. Of note, there were no pediatric reports.

Table 2: Vaxchora VAERS reports during December 23, 2020, to June 30, 2025

Age	Serious Non-Fatal* US	Serious Non-Fatal* Foreign	Deaths US	Deaths Foreign	Non-Serious US	Non-Serious Foreign	Total Reported US	Total Reported Foreign
≥ 18 years	2	0	1	0	29	1	32	1
Unknown**	0	0	0	0	7	8	7	8
Total	2	0	1	0	36	9	39	9

*Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability or otherwise medically important conditions (OMIC).

Reviewer Comment: Upon reviewing the case narratives for the non-serious reports, age-related information was retrieved for eight of the "unknown" age cases. Therefore, among non-serious cases, there were a total of 36 US cases (33 adults, 3 age unknown) and 9 foreign cases (5 adults, 4 age unknown). (Please see additional discussion of non-serious reports in section 6.2.3 of memorandum.)

6.2.1 Deaths

There was one adult death reported during the safety review period, described below. No new safety concerns were identified from review of this case.

- A 64 y/o female with a significant past medical history of COPD reportedly received Vaxchora, and "site" of administration is listed as the "right arm." As per the report, one day post-vaccination, she "had pain in the injection site and her shoulder and developed pneumonia after about a week." She experienced progressively worsening pain at the injection site as well as in her shoulder. Six days post-vaccination, the patient was found non-responsive, unable to be revived by EMS and pronounced dead. This patient's death certificate listed her cause of death as community acquired pneumonia and no autopsy was performed.

Reviewer Comment
Vaxchora is indicated for oral administration only (see section 1.2 of memorandum). It is supplied as a single dose carton containing two packets – a Buffer Component Packet and an Active Component Packet; each packet states that it is for "oral administration." It is important to note that the contents of the active component packet are lyophilized, and Vaxchora is prepared by reconstituting the buffer component in 100mL of bottled water (purified, spring, or sparkling [carbonated]), then adding the active component. After preparation, a single dose of Vaxchora for an adult is 100 mL suspension for oral administration.

From the information provided in the report, it may seem that the patient received an injectable product, leading to injection site and shoulder pain. However, given how this

vaccine is supplied and labeled instructions regarding dosage and administration, it seems unlikely that the provider would transfer material from one or both of the component packets into a syringe for IM administration. There were no reports of incorrect route of administration from a review of either serious reports or non-serious reports, with PTs displayed in Table 4 (section 6.2.3 of memorandum).

The patient's history of underlying COPD and onset of pneumonia point towards an infectious etiology contributing to her death. The official cause of death was attributed to community acquired pneumonia as stated on her death certificate.

6.2.2 Serious Non-fatal Reports

During the safety review period, there were 2 U.S. adult non-fatal serious reports, described below. No new safety concerns were identified from review of these cases.

- A 78-year-old female with a past medical history of hypertension, high cholesterol, anxiety and depression, received Vaxchora concurrently with Pfizer-BioNTech COVID-19 Vaccine (previously authorized under Emergency Use authorization and subsequently approved as Comirnaty). She developed pain in her left arm (Pfizer-BioNTech COVID-19 Vaccine had been administered in the left arm) which progressed to shoulder pain, and she subsequently went to the emergency room where she was prescribed pain medication.

  Reviewer Comments: Given that Vaxchora is for oral administration only, the AE related to left arm and shoulder pain is unrelated to Vaxchora. Pfizer-BioNTech COVID-19 Vaccine was administered by intramuscular injection. Pain, redness, swelling at injection site, muscle pain and joint pain are labeled events for Comirnaty.

- An 80-year-old male with a past medical history of diabetes, hypertension, asymptomatic HIV, hyperlipidemia, and chronic renal insufficiency received Vaxchora concurrently with Pfizer-BioNTech COVID-19 Vaccine. Six months post-vaccination, he developed facial pain associated with trigeminal neuralgia. No other clinical information was provided.

  Reviewer Comments: There is a lack of temporal association (onset of symptoms 6 months post-vaccination), and underlying conditions present confounders. Potential risk factors for trigeminal neuralgia in this patient include age >50 years, diabetes, and hypertension.

6.2.3 Non-serious Reports

During the safety review period, there were 36 U.S. non-serious reports and 9 foreign non-serious reports. There were no reports in pediatric individuals.

Table 4 below lists the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs), occurring with a frequency ≥3 reports in non-serious reports. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 4: Most frequently reported PTs in Non-Serious Reports

Preferred Term (PT)	**# Non-serious Reports**	**Label Status** *USPI updated February 2025*
Headache	7	Labeled (6.1 Clinical Trials Experience)
Pyrexia	6	Labeled as *Fever* (6.1 Clinical Trials Experience)
Pain	5	Unlabeled
Arthralgia	4	Unlabeled
Chills	4	Unlabeled
Hyperhidrosis	4	Unlabeled
Injection Site Pain	4	Unlabeled
Product Administered to Patient of Inappropriate Age	4	Unlabeled
Fatigue	3	Labeled as *Tiredness (*6.1 Clinical Trials Experience)
Influenza Like Illness	3	Unlabeled
Nausea	3	Labeled (6.1 Clinical Trials Experience)
Oral administration complication	3	Unlabeled
Product packaging issue	3	Unlabeled
Syncope	3	Unlabeled
Vomiting	3	Labeled (6.1 Clinical Trials Experience)

Reviewer comments: Overall, there are few reports for each PT. The most frequently reported PTs are labeled events or related to a labeled event or represent non-specific events.

Pain is non-specific and may also represent labeled events *abdominal pain* or *headache*. *Arthralgia* and *hyperhidrosis* are non-specific. *Influenza like illness,* which appears in few reports, is commonly occurring and may represent infectious etiology. *Chills* may be related to labeled event *fever*. *Injection site pain* represents concomitant intramuscular administration of other products.

Oral administration complication involved two reports related to individuals who ate food soon after vaccination. Of note, the USPI section *2 Dosage and Administration – Restrictions on Eating and Drinking* and section *7 Drug Interactions – Food and Drink*, instruct recipients to avoid eating or drinking for 60 minutes before and after oral ingestion of Vaxchora. The third report involved an individual who received amoxicillin prior to Vaxchora (section USPI Section 7 *Drug Interactions – Concomitant Vaccines or Medications* describes interaction with antibiotics and provides instructions to avoid concomitant administration of Vaxchora with systemic antibiotics and to not administer

Vaxchora to patients who have received oral or parenteral antibiotics within the previous 14 days).

Product packaging issue involved reports of “open flaps” in the packaging; no vaccine was administered to patients and thus there were no AEs.

Reports of *syncope* involved individuals who received oral Vaxchora as well as other intramuscular concomitant vaccines. Syncope (fainting) may occur in association with administration of injectable vaccines.

The unlabeled PT *Product Administered to Patient of Inappropriate Age* does not represent a clinical adverse event, and most reports involve administration to individuals >64 years of age.

6.3 Data Mining

Data mining was performed to evaluate whether any reported events following the use of Vaxchora were disproportionally reported compared to other vaccines in the VAERS database. The background database contains VAERS reports since 1990. Disproportionality alerts (EB05>2; EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean) do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signals Management with the US VAERS Vac Name run for Cholera (Vaxchora) with a data lock date of September 11, 2025, identified the following PTs (displayed below) with a disproportional reporting alert (EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean).

Table 5: Data Mining Results

Preferred Term (PT)	# Reports	Label status
Labelled drug-food interaction medication error	4	Unlabeled
Oral administration complication	6	Unlabeled
Product administered to patient of inappropriate age	15	Unlabeled

Reviewer comments: The above PTs involved non-serious reports. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs. Some of these PTs were previously discussed in section 6.2.3.

Most reports for *Labelled drug-food interaction medication error* and *oral administration complication* involved individuals who ate food soon after vaccination. Most vaccines are administered intramuscularly; disproportional reporting alerts for PTs involving oral administration with Vaxchora can be expected because data mining compares the reporting proportions for Vaxchora to the reporting patterns of all other vaccines. *Product administered to patient of inappropriate age* does not represent a clinical AE,

and most reports involved off-label use in individuals >64y (discussed previously in section 6.2.3 of memorandum).

No new safety issue was identified from review of disproportionality alerts.

6.4 Periodic Safety Reports

The manufacturer's post-marketing periodic safety reports for Vaxchora were reviewed. The AEs reported were consistent with those seen in VAERS. No additional safety issues were identified, and no actions were taken by the sponsor for safety reasons.

7 LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on September 6, 2025, for peer-reviewed literature, with the search term "Vaxchora" and "safety" limited by human species, and dates from PAC trigger (December 23, 2020) to date of search (September 6, 2025), retrieved 38 publications of which 2 pertained to safety. No new safety concerns for Vaxchora were identified in the review of these publications, summarized in the table below:

Publication	Authors' Safety Conclusion
McCarty J, Bedell L, De Lame PA, Cassie D, Lock M, Bennett S, Haney D. Update on CVD 103-HgR single-dose, live oral cholera vaccine. Expert Rev Vaccines. 2022 Jan;21(1):9-23. doi: 10.1080/14760584.2022.2003709. Epub 2021 Dec 27. PMID: 34775892.	Vaxchora vaccine is well tolerated in all age groups. Most of the solicited adverse reactions reported in the clinical trials were mild, lasted 2 days or less, and included tiredness, headache, abdominal pain, nausea/vomiting, lack of appetite, fever, and diarrhea, with only diarrhea, mostly mild, seen more frequently in vaccine vs placebo recipients. No vaccine-related serious adverse events were reported in any trial. In addition to these clinical trial data, 68,648 doses of Vaxchora vaccine have been sold in the United States since 2016 and no new safety signals have been identified.
El Hayek P, Boueri M, Nasr L, Aoun C, Sayad E, Jallad K. Cholera Infection Risks and Cholera Vaccine Safety in Pregnancy. Infect Dis Obstet Gynecol. 2023 May 22;2023:4563797. doi: 10.1155/2023/4563797. PMID: 37260611; PMCID: PMC10228220.	Cholera epidemics continue to threaten the lives of patients of all ages and particularly vulnerable population notably pregnant women, neonates, children, and immunocompromised patients. As the literature suggests, severe dehydration caused by cholera infection could affect the pregnancy course and lead to devastating outcomes for the mother and baby. Stillbirth and spontaneous miscarriages were reported following severe maternal dehydration and diarrhea due to cholera infection. Vaccines are shown to be safe and effective in pregnancy.

8 CONCLUSION

This postmarketing pediatric safety review was triggered by the approval of the sBLA 125597/123 on December 23, 2020, for use of Vaxchora in individuals 2 years to <18

years of age traveling to cholera-affected areas. Review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Vaxchora does not indicate any new safety concerns. Adverse events were generally consistent with the safety data in pre-licensure studies and listed in the label. There were no pediatric AE reports, and few reports overall during the safety period. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Vaxchora.