



Recommendation to Grant Tropical Diseases Priority Review Voucher

STN: BL 125597/0

Product: Cholera Vaccine, Live, Oral

Trade Name: VAXCHORA

Sponsor: Pax Vax Bermuda Ltd.

Indication: For active immunization against disease caused by *Vibrio cholerae* serogroup O1 in adults 18 through 64 years of age traveling to cholera-affected areas.

Date of Submission: October 16, 2015

From: Goutam Sen, Ph.D., Chair of the file

Through: Wellington Sun, M.D., Director, DVRPA

To: The file, STN: 125597

Background

IND 15010 "Cholera (*Vibrio cholerae* O1 Inaba with Toxin A subunit gene deletion; PXVX0200) Vaccine, Live, Attenuated, Oral" was submitted on February 10, 2012. On December 20, 2012, development of PXVX0200 investigational cholera vaccine was granted Fast Track designation. When the VAXCHORA Biologics License Application (STN:125597) was submitted the applicant requested priority review. The application was granted priority review because, 1) VAXCHORA prevents cholera, which is a serious disease and, 2) if licensed, VAXCHORA would be a significant improvement in effectiveness for prevention of cholera for U.S. travelers to cholera-affected areas.

In the BLA application, PaxVax stated that their application for VAXCHORA was eligible for a Tropical Disease Priority Review Voucher upon approval, because:

1. VAXCHORA is intended for the prevention of a listed tropical disease, namely cholera.
2. The application is submitted under section 351 (a) of the FD&C Act.
3. VAXCHORA (genetically modified CVD 103-HgR vaccine strain) is a new molecular entity, which has never been approved or licensed by FDA.
4. VAXCHORA is eligible for priority review.

Reviewer's Comments:

U.S. residents traveling to cholera endemic or epidemic areas are at risk of cholera because: 1) residents are typically cholera-naïve; 2) strategies to contain and control cholera are not fully implemented in many under-developed regions, creating opportunities for cholera to persist; 3) the Center for Disease Control (CDC)- and World Health Organization (WHO)- recommended prevention practices may not be consistently adhered to; and 4) a U.S. licensed vaccine against cholera is not available.

Currently there are two inactivated two-dose cholera vaccines (Dukoral® [Crucell; Leiden, The Netherlands] and Shanchol™ [Shantha Biotechnics; Hyderabad, India]) available outside the U.S. Neither of these products is licensed in the U.S. Killed whole cell cholera vaccines were previously licensed in the U.S., however, these are no longer manufactured.

VAXCHORA (Cholera Vaccine, Live, 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 94% of the catalytic domain sequence of both copies of the *ctxA* gene. A mercury resistance operon was inserted into a hemolysin gene locus (*hlyA*) to enable differentiation of the vaccine strain from wild type *V. cholerae* O1. VAXCHORA is prepared by reconstituting the buffer component in 100 mL of purified bottled water and adding the bacterial component (lyophilized *V. cholerae* CVD 103-HgR). After preparation, a single dose of VAXCHORA is 100 mL.

PaxVax has conducted four clinical studies. Two Phase 3 clinical studies supported effectiveness (PXVX-VC-200-003 and PXVX-VC-200-005), one Phase 3 clinical study demonstrated manufacturing consistency (PXVX-VC-200-004), and one Phase 1 study provided shedding and transmission data (PXVX-VC-200-002).

Study PXVX-VC-200-003 was a randomized, double-blind, placebo-controlled challenge Phase 3 study which enrolled subjects 18-45 years of age. The data provided in the VAXCHORA BLA show that the protective efficacy of VAXCHORA against moderate to severe diarrhea following challenge with virulent *V. cholerae* O1 El Tor Inaba was 90.3% (95% CI; 62.7% - 100.0%) at 10 days and 79.5% (95% CI; 49.9% - 100.0%) at 3 months post-vaccination. Exploratory data from the challenge study showed that seroconversion (\geq four-fold rise from baseline in serum vibriocidal antibody against a classical Inaba *V. cholerae*) at 10 days post-vaccination was associated with protection against moderate to severe cholera in both the 10-Day and 3-Month challenge groups. Therefore, seroconversion 10 days after vaccination was selected as the immunologic parameter for bridging effectiveness to adults 46-64 years of age.

PXVX-VC-200-004 was a lot consistency and safety study conducted in subjects 18- 45 years of age. Study PXVX-VC-200-005 was a randomized, double-blind, placebo-controlled Phase 3 safety and immunogenicity study conducted in subjects 46 through 64 years old. Effectiveness of VAXCHORA in this population was based on a comparison to the immune response of subjects 18 - 45 years of age enrolled in Study PXVX-VC-200-004. The primary objectives

were to demonstrate that: 1) seroconversion as measured by classical Inaba vibriocidal antibody 10 days post-vaccination in individuals 46 through 64 years of age was non-inferior to the corresponding seroconversion rate 10 days post-vaccination in Study PXVX-VC-200-004 and, 2) the lower bound of the 2-sided 95% CI on seroconversion by classical Inaba vibriocidal antibody 10 days post-vaccination was greater than 70% in persons 46 through 64 years of age. Seroconversion was defined as a 4-fold or greater rise in vibriocidal antibody level from baseline to 10 days post-vaccination. Both primary objectives were met: the lower limit of the 2-sided 95% CI on the difference in seroconversion rates (older adults minus younger adults) was -6.7%, greater than the pre-specified non-inferiority margin of -10%. The lower bound of the two sided 95% CI on seroconversion in older adults was 86.4%.

Serum vibriocidal antibody against the three major subtypes of *V. cholerae* not contained in the vaccine, namely classical Ogawa, El Tor Inaba and El Tor Ogawa, was measured in the challenge study (PXVX-VC-200-003) and the study in 46 through 64 year old adults (PXVX-VC-200-005). The percentages of 18 through 45 year old vaccine recipients in study PXVX-VC-200-003 who seroconverted against each of the four major biotypes/serotypes of *V. cholerae* serogroup O1 at 10 days post-vaccination ranged from 87.1% (classical Ogawa) to 91.4% (El Tor Inaba). Among adults 46 through 64 years of age, seroconversion rates to each of the four major biotypes/serotypes 10 days post-vaccination ranged from 71.4% (El Tor Ogawa) to 91.0% (El Tor Inaba).

The safety of VAXCHORA was evaluated in adults 18 through 64 years of age across four clinical studies. A total of 3235 VAXCHORA recipients and 562 placebo recipients contributed to the safety database. The safety data reviewed raised no safety concerns that would preclude licensure. Within 6-months post-vaccination, 20 (0.6%) VAXCHORA recipients and 3 (0.5%) placebo recipients reported a serious adverse event. No vaccine-related serious adverse events occurred, and no signals of serious risk were identified. One death due to suicide in a 38 year old occurred 84 days after receipt of VAXCHORA; this death was not considered to be caused by vaccination.

The challenge study approach to establish efficacy of VAXCHORA to prevent cholera in travelers to cholera affected areas was discussed and accepted at a meeting of the Vaccines and Related Biologics Advisory Committee in 1998.

Recommendations for Tropical Diseases Voucher

VAXCHORA is intended for the prevention of a listed tropical disease, the licensing application is submitted under section 351 of the PHS Act and the active ingredient has not been previously approved. The active ingredient of VAXCHORA is a genetically modified live *V. cholerae*. A genetically modified *V. cholerae* strain has not been approved in any other application under section 351 of the PHS Act. As VAXCHORA meets all the criteria for a Tropical Disease priority review voucher, on behalf of the review committee, I recommend granting PaxVax's BLA 125597 application for a Tropical Disease priority review voucher.

FDA Guidance

Regarding Tropical Diseases Voucher Eligibility, the October 2008 Draft Guidance for Industry "Tropical Disease Priority Review Voucher"

(<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM080599.pdf>) states that “an application is eligible to receive a tropical disease voucher if the application is for a listed tropical disease, the application must be submitted under section 505(b)1 of the FD&C act or section 351 of the PHS act, the drug must not contain any active ingredient that had been previously approved under section 505(b)1 of the FD&C act or section 351 of the PHS act, and the application must qualify for a priority review”.

Concurrence Page

Application Number: BLA 125597/0

REVIEW TYPE: Recommendation for Priority Review and Tropical Diseases Priority Review Voucher

History:

Sen, G: 4/14/2016

Mongeau, T: 4/15/2016

Daugherty, J: 4/27/16

Sun, W: 4/27/16

Finn, T: 5/24/16

Joneckis, C: 5/31/16

Farizo, K: 6/1/16

Concurrence:

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