



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE MEMORANDUM

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CBER, FDA

To: Qun Wang, Ph.D.
Chair, Review Committee
Office of Vaccine Research and Review (OVR)

Through: Adamma Mba-Jonas, MD, MPH
Branch Chief, PB-1

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Deputy Director, DPV

Subject: Review of Pharmacovigilance Plan

Sponsor: Ferring Pharmaceuticals, Inc.

Product: fecal microbiota, live (REBYOTA)

Application Number: BLA 125739.0

Proposed Indication: to reduce the recurrence of *Clostridioides difficile* infection (CDI)
in adults following antibiotic treatment for recurrent CDI

Submission Date: 11/30/2021

Action Due Date: 11/30/2022

1 INTRODUCTION

1.1 Objective

The purpose of this review is to assess the adequacy of the Sponsor's plan for passive and active surveillance for fecal microbiota.

1.2 Materials reviewed

- Study reports for clinical trials
- Integrated summary of safety
- Pharmacovigilance Plan (PVP), original and revised
- Draft package insert (PI)
- Responses to Information Requests (please see below)

2 PRODUCT INFORMATION

2.1 Product description

Per the proposed PI:

“REBYOTA is a pre-packaged single-dose 150 mL microbiota suspension for rectal administration containing diverse spore-forming and non-spore-forming bacteria, including Bacteroides, biologically sourced, health screened, and pathogen tested to ensure patient safety.

REBYOTA is an opaque suspension. Each dose of REBYOTA contains (b) (4) CFU with viable Bacteroides solution containing Polyethylene Glycol in Saline. REBYOTA is not an antibiotic.”

2.2 Indication

Per the proposed PI:

“Reduce the recurrence of Clostridioides difficile infection (CDI) in adults following antibiotic treatment for recurrent Clostridioides difficile infection (rCDI).”

3 PERTINENT REGULATORY HISTORY

RBX2660 is not currently licensed in any country.

4 SAFETY DATA SUBMITTED BY THE SPONSOR

4.1 Clinical studies

The Sponsor has submitted data from six clinical studies of RBX2660 in individuals 18 years of age and older.

Trial 2013-001

Phase 2, prospective, multicenter, open-label, noncontrolled trial designed to assess the safety of RBX2660 in the US

Trial 2014-01

Phase 2B, prospective, multicenter, randomized, double-blind, placebo-controlled, 3-arm trial designed to assess efficacy and safety of RBX2660 in the US and Canada

Trial 2015-01

Phase 2, prospective, multicenter open-label trial designed to assess the efficacy and safety of RBX2660 compared to historical control in the US and Canada

Trial 2017-01

Phase 3, prospective, multicenter, randomized, double-blind, placebo-controlled trial designed to assess efficacy and safety of RBX2660 in the US and Canada

Trial 2019-02

retrospective, multicenter, safety and tolerability trial of RBX2660 in individuals who did not qualify for the trials (Enforcement Discretion)

Trial 2019-01

Phase 3, prospective, multicenter, open-label trial designed to evaluate the safety and tolerability of RBX2660 in the US and Canada; includes patients with ulcerative colitis, Crohn's disease, or microscopic colitis. As of 5/13/2022, the study is ongoing.

The Sponsor has submitted safety data from 978 people who received RBX2660: 751 (76.8%) completed 6-month follow-up, and 182 (18.6%) completed 24-month follow-up.

In the placebo-controlled trials, the placebo contained normal saline and no polyethylene glycol.

4.2 Adverse events

Data in the original submission and Amendments 7, 19, and 23 showed imbalances in total adverse events (AEs), as well as serious adverse events (SAEs). However, in those tables, results for RBX2660 included people who were randomized to received placebo and then crossed over to RBX2660. On 9/26/2022, CBER sent an Information Request and asked the Sponsor to provide AE data for people who had crossed over, including whether the AE occurred while the person was taking placebo or RBX2660; the response was submitted in Amendment 41.

Forty-eight people were randomized to placebo but, because of continuing/worsening symptoms, they crossed over and received RBX2660. Per Ferring:

“In the Placebo crossover group (Placebo+RBX2660 columns), the safety follow-up duration was shorter for subjects in the placebo group since they experienced a recurrence of CDI (blinded treatment failure) and opted to receive an unblinded course of RBX2660. These subjects completed less than 8 weeks of safety follow-up during the placebo exposure period whereas up to 6 months of safety follow-up was completed in the unblinded RBX2660 exposure period.

Additionally, the RBX2660 only group (total N=930) included subjects who received 1 treatment course of RBX2660 (N=763; of which N=193 received blinded RBX2660), and those who received an unblinded course of RBX2660 (one or two additional enemas; N=167) following a recurrence of CDI. Therefore, the events in this group included those associated with rCDI symptoms/complications and treatments administered prior to the unblinded course of RBX2660.”

The table below summarizes AEs that are numerically imbalanced. However, the total number of enrolled subjects was small, and significance testing was not performed.

Table. Adverse Events^a after RBX2660 and Placebo

Adverse Event	RBX2660 Only N = 930	Placebo + RBX2660 ^b N = 48		Placebo Only N = 83
		Placebo	RBX2660	
Gastrointestinal				
<i>C. difficile</i> colitis	8 (0.9) <i>8 (0.9)</i>	--	--	--
<i>C. difficile</i> infection	27 (2.9) <i>25 (2.7)</i>	--	--	1 (1.2) <i>0</i>
Infections other than <i>C. difficile</i>				
Bacteremia	4 (0.4) <i>4 (0.4)</i>	--	--	--
Cystitis	7 (0.8) <i>0</i>	--	1 (2.1) <i>0</i>	--
Pneumonia	13 (1.4) <i>6 (0.6)</i>	1 (2.1) <i>0</i>	1 (2.1) <i>0</i>	1 (1.2) <i>0</i>
Urinary tract infection	69 (7.4) <i>7 (0.8)</i>	1 (2.1) <i>0</i>	1 (2.1) <i>1 (2.1)</i>	4 (4.8) <i>0</i>
Other medical				
Congestive heart failure	11 (1.2) <i>9 (0.9)</i>	--	--	--
Chronic obstructive pulmonary disease	15 (1.6) <i>7 (0.8)</i>	--	--	--
Psychiatric				
Anxiety	26 (2.8) <i>1 (0.1)</i>	--	--	1 (1.2) <i>0</i>
Depression	21 (2.3) <i>1 (0.1)</i>	--	--	--

The table is adapted from Sponsor's Tables 1-4 in Amendment 41 (response to Information Request).

^aIn each cell, numbers and percentages in plain text represent the total for that adverse event, and the italicized numbers represent serious adverse events.

^bForty-eight people received placebo and then crossed over to RBX2660, but they had different AEs at different times (i.e., while on placebo or while taking RBX2660). Therefore only the total denominator is presented.

Gastrointestinal: *C. difficile* infection and colitis occurred almost exclusively after RBX2660, and all of the serious cases occurred after the investigational product.

Infections other than C. difficile: Bacteremia occurred only after RBX2660, and all cases were serious. Pneumonia was similar in the treatment groups, but serious cases occurred only after the investigational product. Urinary tract infections (UTIs) were more common after RBX2660, and serious cases occurred only after the investigational product.

Other medical events: Congestive heart failure (CHF) occurred only after RBX2660, and a large majority of cases (82%) were serious. Similarly, chronic obstructive pulmonary disease (COPD) occurred only after the investigational product, and nearly half of cases (47%) were serious.

Psychiatric: Anxiety was twice as frequent after RBX2660, and all cases of depression occurred after the investigational product.

Reviewer comment:

RBX2660 recipients and placebo recipients differed not only in their exposure to microbiota, but also to polyethylene glycol (PEG). The presence of microbiota might explain the greater frequency of general gastrointestinal signs and symptoms (e.g., diarrhea and abdominal distension) after RBX2660, but it does not explain the other imbalances.

Anaphylaxis after PEG exposure has been described¹, but it is not clear whether PEG could cause or contribute to other adverse events, such as CHF, COPD, or infections. Based on the AE data and narratives that the Sponsor has provided, it is difficult to ascribe causality or to assess whether a causal association with PEG and/or RBX2660 is biologically plausible.

DPV defers to the clinical reviewer for more detailed review of prelicensure safety data. Per the OVR clinical reviewer, “Overall safety evaluation of the clinical program did not reveal a trend of adverse events related to the RBX2660 enema. No substantive safety issues have been identified that would preclude licensure.”

5 SPONSOR’S PVP

5.1 Overview of pharmacovigilance

Per the Sponsor: *“The safety profile of RBX2660 characterized above was shown to be not associated with any unexpected severe or serious adverse reactions across a varied rCDI patient population, including aged, immunocompromised, and severely ill patients. There are no important identified risks. The important potential risk identified for RBX2660 of the transmission of infection is theoretical and not was not seen in clinical trials. The safety of RBX2660 will be continuously monitored including preparation and submission of expedited reports and aggregate Periodic Adverse Drug Experience reports.*

¹ Sellaturay et al. Polyethylene Glycol-Induced Systemic Allergic Reactions (Anaphylaxis). J Allergy Clin Immunol Pract. 2021 Feb;9(2):670-675.

Important Identified Risks: not applicable

Important Potential Risks: transmission of infection

Important Missing Information: none

Routine Pharmacovigilance Activities

Based on the described Benefit-Risk evaluation, no further pharmacovigilance activities beyond routine pharmacovigilance, including adverse reaction reporting and signal detection are planned.

The Phase 3 Trial 2019-01 is an ongoing (open for enrollment), prospective, multicenter, open-label trial designed to evaluate the safety and tolerability of RBX2660 in an rCDI population that is broader and more inclusive than prior RBX2660 studies.

No additional pharmacovigilance activities are required at this time.”

Please see section 8 of memo for an assessment of the PVP and section 9 of memo for recommendations regarding enhanced pharmacovigilance.

5.2 Postmarketing study

In the original submission, the Sponsor did not propose any postmarketing studies. In response to an Information Request, Ferring submitted a protocol synopsis for a General Safety Surveillance Study (GSS) in the postmarketing period, “A multi-center, single-arm, post-marketing safety study of REBYOTA (microbiota suspension) in adults with recurrent *Clostridioides difficile* infection.” Briefly, the company proposed a multi-center, single-arm study in approximately 200 individuals. Primary endpoints would include the number and proportion of treatment-emergent adverse events (TEAE) within 6 months after treatment with RBX2660. Secondary endpoints would include the number and proportion of adverse events of special interest (AESI) within 6 months after treatment with RBX2660; proposed AESIs would include septic shock, toxic megacolon, colonic perforation, and emergency colectomy.

The review team had concerns that a single-arm observational study of 200 recipients of REBYOTA might have limited ability to yield meaningful safety information. CBER sent comments to the Sponsor and recommended increasing the sample size, altering the study design to include a comparator, and considering alternative strategies for a more robust study design, such as the use of population-based data sources.

The Sponsor submitted a new study protocol entitled, “A Population-based Post-Marketing Safety Surveillance Study of REBYOTA (microbiota suspension) in Adults with Recurrent *Clostridioides difficile* Infection (rCDI),” which would be conducted using a large US healthcare database (e.g., MarketScan, Optum, Medicare, or another administrative claims database) following feasibility assessment. Regarding sample size, the Sponsor projects that approximately 672 patients would be treated with REBYOTA for rCDI within 12 months, 1,344 patients within 24 months, and 2,016 patients within 36 months after start of utilization in this database. The

primary objective is to compare patient demographics, clinical characteristics, and safety outcomes. (relative risks of AESIs) after REBYOTA compared with the standard of care and antibiotics. REBYOTA. The primary endpoint is the incidence of AESIs up to month 6 after REBYOTA or comparator treatment(s). Final protocol submission is planned for 03/31/2024 and final study report is planned for 04/30/2027.

Reviewer comments: While the population-based study design will capture a larger sample size (estimated 2016 patients at 3 years after product utilization in the database) and have a comparator, it is unclear at this time if the study design will be feasible in an administrative claims database. The review team determined that this would be a voluntary Sponsor study, and Ferring was instructed to provide study status updates, and assessment of any safety signal identified by this study, in periodic safety reports.

6 DPV REVIEW OF DRAFT PI

There is no postmarketing experience with this product.

7 ADVISORY COMMITTEE

On September 22, 2022 the Vaccines and Related Biological Products Advisory Committee (VRBPAC) reviewed data supporting the licensure of RBX2660. Regarding safety, the committee voted 12 in favor and 4 against, with one abstention.

Several VRBPAC members stated that additional information about benefit-risk would be helpful. However, quantitative modeling would involve numerous uncertainties and assumptions. VRBPAC members suggested that a postmarketing study to evaluate safety and effectiveness might provide additional information. Additionally, the PI could convey uncertainties around benefit/risk (e.g., potentially increased risk of infection complications in immunocompromised individuals). Finally, the PI could include a general Precaution regarding the limitations of donor screening, along with the Warning that the Sponsor has proposed regarding hypersensitivity.

8 DPV ASSESSMENT

Several adverse events, including serious ones, were numerically imbalanced in the clinical trials. Without tests of statistical significance, it is difficult to determine the importance of these imbalances. The OVR clinical reviewer has stated that no substantive safety issues have been identified that could preclude licensure. DPV comments are as follows:

- Based on the available data from clinical studies thus far, DPV agrees that there are no Important Identified Risks.
- Regarding potential risks, DPV notes that UTIs were more frequent after RBX2660 than placebo and, most concerning, serious UTIs occurred only in the treatment group. Since

Escherichia coli (*E. Coli*) is a component of fecal microbiota and a major cause of UTIs, an association of RBX2660 and UTI could be biologically plausible. The planned GSS would provide an opportunity to collect information about UTIs as TEAEs. However, given the numerical imbalance noted during the trials and the biologic plausibility of a causal association with FMT, UTI should be evaluated as an AESI in the GSS.

- In addition, there is a potential risk of FMT-associated transmission of enteropathogenic *E. coli* (EPEC) or Shigatoxin-producing *E. coli* (STEC). In 2020, FDA was notified that six people who had received a different Sponsor's FMT developed infections caused by EPEC (two patients) or STEC (four patients). Four of the six patients required hospitalization, and the product was recalled. Transmission of EPEC or STEC following RBX2660 enema is biologically plausible. DPV recommends modifying the PVP to include pharmacovigilance measures for monitoring and reducing the risk of FMT-associated transmission of infection. Given the potential severity of EPEC and STEC and the biologically plausible association with FMT, these AEs should be evaluated as AESIs in the GSS.
- If post-treatment *C. difficile* infection and colitis represented confounding by indication, then cases should have occurred in each of the study arms, yet they occurred only after RBX2660. However, as these events could represent treatment failure, DPV defers to OVRP regarding further evaluation of treatment-associated *C. difficile*.
- DPV notes that the VRBPAC recommended that the PI include a Precaution regarding limitations of donor screening, in addition to Warning about hypersensitivity. DPV defers to OVRP on the final language in the PI.
- The association of CHF, COPD, anxiety, and depression with RBX2660 remains unclear but should be monitored as part of routine postmarketing safety surveillance.
- DPV asked the Sponsor to update the PVP to include *Important Missing Information: use in pediatric populations, use in pregnant or lactating women, and use in immunocompromised individuals*. The Sponsor updated the PVP as requested.
- DPV asked the Sponsor to conduct enhanced pharmacovigilance for 3 years after product licensure and to submit expedited 15-day reports for all SAEs regardless of expectedness. DPV also asked the Sponsor to provide aggregate analysis and updates in periodic safety reports for all SAEs, and any AE (regardless of seriousness) in individuals who receive REBYOTA while pregnant or lactating; in individuals who are < 18 years of age; in immunocompromised individuals. The Sponsor has provided written acknowledgement of the enhanced pharmacovigilance requirements. Periodic safety reports will include patient exposure data.
- The Sponsor's intent to establish a voluntary GSS, should the product be approved, is acceptable. When the Sponsor submits a full protocol for a general safety surveillance postmarketing study, DPV will review it, discuss with OVRP as needed, and provide comments. The list of AESIs will likely need to be expanded to include UTI, EPEC, and STEC. General monitoring for COPD, CHF, depression, and anxiety is adequate. Plans for collecting demographic and clinical data and other relevant information will be finalized in the post approval period.

Data available at this time do not suggest any safety signals that warrant a Risk Evaluation and Mitigation Strategy or safety-related Postmarketing Requirements. There are no safety-related Postmarketing Commitments for this product. At this time, the Sponsor's proposed plans for routine surveillance and a voluntary GSS are adequate, with the addition of DPV-recommended enhanced pharmacovigilance.

9 OBPV/DPV RECOMMENDATIONS

Based on review of the premarket clinical safety database and the Sponsor's proposed PVP, OBPV/DPV recommends the following for postmarketing safety monitoring of REBYOTA:

- a. Routine pharmacovigilance: Adverse event reporting in accordance with 21 CFR 600.80 and quarterly periodic safety reports for 3 years and annual thereafter.
- b. Enhanced pharmacovigilance (in addition to complying with the requirements under 21 CFR 600.80): Expanded adverse experience reporting to the FDA Adverse Event Reporting System (FAERS) for 3 years following product licensure, as follows:
 - The Sponsor will submit all SAEs (regardless of expectedness) as expedited 15-day alert reports to FAERS.
 - In the narrative summary of periodic safety reports, the Sponsor will include aggregate analysis and assessment for:
 - all SAEs;
 - AEs (regardless of seriousness) in individuals who receive REBYOTA while pregnant or lactating; in individuals who are < 18 years of age; in immunocompromised individuals.
- c. Voluntary Sponsor study for postmarketing safety surveillance: The Sponsor will conduct a GSS using a claims-based database, as described above. OBPV/DPV will review Sponsor study updates to be provided in periodic safety reports.

Information Requests

On the following dates, DPV requested additional information from the Sponsor and found the responses to be adequate.

Information Request		Amendment / Response	
IR #2 12/1/2021	Request PVP	Amendment #6 12/14/2021	contains PVP
IR #3 12/16/2021	Request more information about PVP	Amendment #7 12/21/2021	contains aggregate numbers of cases of Preferred Terms for all AEs, SAEs, and deaths
		Amendment #19 5/20/2022	contains updated table of TEAEs
IR #14 6/8/2022	Request more information about PVP	Amendment #23 6/22/2022	contains number of cases of Preferred Terms for total AEs, SAEs, and deaths
IR #18 6/8/2022	Request more information about PVP	Amendment #28 6/22/2022	contains updated PVP
IR #27 9/26/2022	Request AE aggregate numbers for three mutually exclusive groups: (1) subjects who received only RBX2660 (i.e., never received placebo), (2) subjects who received placebo and crossed over to RBX2660, (including how many events occurred while the person was on placebo and how many after the cross-over), and (3) subjects who received only placebo (i.e., did not cross over to RBX2660)	Amendment #41 10/3/2022	contains number of cases of Preferred Terms for total AEs, TEAEs, SAEs, and deaths
IR #30 10/14/2022	Request a protocol synopsis for a general safety surveillance postmarketing study that will further characterize the safety profile of RBX2660	Amendment #46 10/21/2022	contains a protocol synopsis for general safety surveillance study
IR #33 10/27/2022	Request updating PVP to include Important Missing Information (pediatric, pregnant/lactating, and immunocompromised individuals)	Amendment #49 11/1/2022	contains updated PVP
IR #35 11/1/2022	Request protocol synopsis describing more robust general safety surveillance study of REBYOTA in the postmarket setting	Amendment #55 11/7/2022	contains a synopsis of a population-based safety surveillance study
IR #38 11/9/2022	Request that periodic safety reports include enhanced pharmacovigilance and updates about the general safety surveillance study	Amendment #58 11/14/2022	acknowledges the requirements