Fecal microbiota, (Rebyota) **March 2023**
Ferring Pharmaceuticals, Inc. **Non-formulary IP/OP**

Efficacy[1]
The primary efficacy analysis of the Phase 3 double blind, RCT (Randomized Controlled Trial), placebo-controlled study 2017-01 (PUNCH CD3) met the second pre-specified statistical success threshold 0.9750 but did not meet the more stringent 0.9993 first specified success threshold.
Prior to performing the analysis, the FDA (Food and Drug Administration) concluded that a posterior finding equivalent to meeting the first specified success threshold would be sufficient to demonstrate substantial evidence of effectiveness. After the primary efficacy analysis only met the second specified success criteria, FDA considered whether the data from the study, as well as the data from the supportive clinical trials would be sufficient to demonstrate substantial evidence of effectiveness. Most FDA committee members thought the clinical data were adequate to support effectiveness of the product. The review team concluded that the data submitted demonstrates substantial evidence of effectiveness for the prevention of recurrent CDI (*Clostridioides Difficile* Infection) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

Safety
Rebyota is manufactured from human fecal matter donated by qualified individuals. The donors and donated stool are screened for transmissible pathogens; however, there may still be a risk of transmitting infectious agents. Additionally, it is possible that Rebyota may contain food allergens; the potential for adverse reactions due to food allergens is unknown.

Uniqueness
Rebyota is the first fecal transplant therapy for recurrent CDI approved by FDA. This therapy is approved for prophylaxis and is not considered for treatment of CDI.

Cost

Cost (AWP)	Cost (AWP)
Rebyota: Fecal microbiota, live-jslm 150 mL (150 mL)	$10,800

Recommendations
Add fecal microbiota live-jslm (Rebyota) to outpatient infusion center and clinic formulary

The authors of this document have no financial relationship with pharmaceutical companies, biomedical device manufacturers, or distributors or others whose products or services may be considered related to the subject matter within.

Introduction[4]
Clostridioides difficile is a spore-forming, toxin-producing, gram-positive anaerobic bacterium that causes antibiotic-associated colitis. It colonizes the human intestinal tract typically after the normal gut flora has been disrupted (frequently in association with antibiotic therapy). Clostridioides difficile infection (CDI) is one of the most common health care-associated infections and a significant cause of morbidity and mortality, especially among older adult hospitalized patients.[6]

C. difficile colonization, defined as detection of the organism in the absence of symptoms, is common, occurring in 4%–15% of healthy adults, up to 21% of hospitalized adults, and 15%–30% of residents in long-term care facilities. Colonization with the organism at the time of admission to the hospital increases the risk of developing CDI 6-fold. Contact with the healthcare environment, advanced age (65 years or older), and antibiotic use are the biggest risk factors for developing an active infection. Although patients in hospitals and long-term care facilities remain at highest risk, of great concern is the rise of community-associated infections, which now account for 35%–48% of CDI diagnoses. Risk factors of community-acquired infections, apart from antibiotic treatment, include White race, cardiac disease, chronic kidney disease, and IBD.[7]

CDI is classified according to disease severity, which influences treatment considerations[4]

- Mild to moderate disease includes patients with ≥3 unformed stools within 24 hours and a positive CDI test.
- Severe disease is identified by a white blood cell (WBC) count of ≥15,000 cells/mm3 or serum creatinine (SCr) >1.5 mg/dL at the time of diagnosis. Patients with severe disease may require hospitalization.
- Fulminant disease includes patients with severe disease plus the presence of hypotension, shock, ileus, or toxic megacolon. Patients with fulminant disease usually require hospitalization.

A challenge of CDI is its tendency to recur after an initial episode. Recurrent CDI is typically defined as the return of diarrhea and a confirmatory positive CDI test within 8 weeks after treatment of an initial episode.
Recurrent CDI is reported to occur in 15% to 30% of cases following treatment. Among patients treated for a first recurrence, a second is reported to happen in about 40% of cases, subsequent recurrences happen in about 45% to 65% of cases.

Pharmacokinetics / Pharmacodynamics[2]
None, not expected to be systemically absorbed.

FDA Approved Indications[2]
Clostridioides difficile infection, prophylaxis: Prevention of recurrence of C. difficile infection (CDI) in patients ≥18 years of age following antibiotic treatment of recurrent CDI.

Not indicated for treatment of CDI.

Guidelines[4,7,8]

In June 2021, the Infectious Diseases Society of America (IDSA), in conjunction with the Society for Healthcare Epidemiology in America (SHEA), produced updated guidelines for the management of CDI in adults. At the same time, the American College of Gastroenterology (ACG) published guidelines on the prevention, diagnosis, and treatment of CDI.

Summary of Guideline Recommendations for Prevention of Recurrent CDI		
Treatment	IDSA/SHEA Guidelines	ACG Guidelines
Oral vancomycin (long-term suppressive therapy)	No comment on use of oral vancomycin for the prevention of recurrent CDI	Recommended in patients with recurrent CDI who are not candidates for FMT, who relapse after FMT, or who require ongoing or frequent courses of antibiotics
Zinplava (bezlotoxumab) infusion	Consider in: Initial episode of CDI and ≥1 risk factor for reoccurance (i.e. severe CDI, ≥65 years of age, or immunocompromised) First recurrent episode for CDI	Consider Zinplava in any patient at high risk of recurrent disease, including patients with an initial episode of CDI
FMT	Recommended for patients with ≥2 recurrences of CDI	Recommended for patients with ≥2 recurrences of CDI

ACG: American College of Gastroenterology; CDI: *Clostridioides difficile* infection; FMT: fecal microbiota transplantation; IDSA, Infectious Diseases Society of America; SHEA, Society for Healthcare Epidemiology in America.

*Based on the 2017 IDSA/SHEA guideline recommendations. The 2021 version of the guidelines provides no update.

Comparison of FMT (fecal microbiota transplant) and Rebyota[4]

	Rebyota	**FMT**
Regulatory Status	FDA approved	Available from independent sources, including stool banks, through IND and IND enforcement discretion
Microbiome Source	Human fecal matter	Human fecal matter
Screening	29 pathogens	Multiple pathogens*
Route of Administration	Enema	Nasoenteric/gastric tube or EGD, colonoscopy, sigmoidoscopy, enema, or orally in capsule form
Storage	Keep frozen at −60 ° to −90 °C or refrigerate at 2 ° to 8 °C for up to 5 days (including thaw time)	Keep frozen at −80 °C, ship overnight in dry ice, and thaw prior to administration

Clinical Trials
PUNCH CD3 (NCT03244644) with Integrated Data from PUNCH CD2 (NCT02299570)

<table>
<tr><th>Study Design</th><th>Methods</th><th>Results</th><th>Conclusions/ Comments</th></tr>
<tr>
<td>Khanna, S. et al, 2022

Trial design
Due to enrollment challenges that precluded the conduct of two placebo-controlled Phase 3 trials, a single placebo-controlled Phase 3 trial (PUNCH CD3) with a primary efficacy analysis that employed a Bayesian hierarchical model formally integrating treatment success rates from a placebo-controlled Phase 2 study (PUNCH CD2) into study PUNCH CD3.

Study PUNCH CD2: Phase 2, double-blind, randomized, placebo-controlled trial in adults ≥18 years old with documented recurrent CDI. 133 participants were randomized 1:1:1 to receive two doses of active comparator, two doses of placebo, or one dose of active comparator and one dose of placebo, administered 7±2 days apart.
Active comparator was administered following an antibiotic washout period of 24–48 hours (PUNCH CD2).

Study PUNCH CD3: Phase 3, double-blind, randomized, placebo-controlled study in adults ≥18 years old with documented recurrent CDI; 289 participants were randomized 2:1 to one dose of REBYOTA 24-72 hrs after antibiotic washout or one dose of placebo.

In both studies, treatment with open-label REBYOTA was an option in the event of treatment failure.

Based on the unmet need, REBYOTA was granted Breakthrough Therapy Status, Fast Track, and Orphan Drug designations by the FDA

Length of trial
8 weeks follow-up 6 months</td>
<td>Inclusion
• ≥18 years of age
• Diagnosis of rCDI (≥1 recurrent episode in PUNCH CD3; ≥2 recurrent episodes in PUNCH CD2).
• Current rCDI episode under control (both trials)
• Patients with food allergies were not excluded.
Exclusion
• History of refractory CDI, inflammatory bowel disease, irritable bowel syndrome, chronic diarrhea, celiac disease, colostomy, active colitis, continued diarrhea despite antibiotic therapy, required antibiotic therapy for another condition, or had a previous FMT

Statistical analysis
The FDA agreed with analysis of the primary endpoint using a Bayesian hierarchical model that dynamically borrowed information about the treatment effect from the previous phase IIb trial, PUNCH CD2,
The advantage of modeling the data jointly in this manner is that if the treatment effect is similar in both studies, a combined analysis can reduce the 1530 S. Khanna et al. amount of uncertainty in the estimate.

This study included two superiority thresholds: (1) posterior probability of superiority > 0.999 selected to control the nominal type I error rate without borrowing at one-sided 0.00125; and (2) posterior probability of superiority > 0.975 selected to control the nominal type I error rate without borrowing at one-sided 0.025. The higher threshold therefore corresponds to a statistically very persuasive finding. The lower threshold provides evidence of a statistically significant phase III trial

Sustained clinical response through 6 months was assessed with frequentist analyses using Pearson's chi-squared test, with a two-sided α = 0.05. Two-sided 95% confidence intervals for the differences in proportions between treatment arms were calculated.</td>
<td>Primary: Absence of CDI diarrhea within 8 weeks of blinded treatment. CDI diarrhea was defined as the passage of ≥3 unformed/loose stools in ≤24 hours for at least 2 consecutive days and a positive stool test for the presence of C. difficile toxin at the time of the diarrhea.
Participants who achieved treatment success at 8 weeks, more than 90% remained free of CDI recurrence through 6 months

Secondary: Sustained clinical response

Treatment Success at 8 Weeks Post-Treatment (mITT)
<table>
<tr><th>Parameter</th><th>Rebyota Mean (95% CI)</th><th>Placebo Mean (95% CI)</th><th>Treatment Effect (Rebyota-placebo) (95% CI)</th></tr>
<tr><td>Model-estimated treatment success (%)</td><td>71 (64, 77)</td><td>57 (48, 67)</td><td>13.1 (2.3, 24.0)</td></tr>
<tr><td>Posterior Probability of Superiority</td><td>-</td><td>-</td><td>0.991*</td></tr>
</table>
*First predefined threshold for superiority was 0.9993; Second Pre-defined threshold for superiority was 0.9750

**Overall, the efficacy results met the second success threshold (posterior probability of superiority 0.9750). However, the efficacy results did not meet the more stringent first success threshold (posterior probability of superiority 0.9993).
<table>
<tr><th>Adverse Reaction</th><th>Rebyota, n =180 n (%)</th><th>Placebo, n = 87, n (%)</th></tr>
<tr><td>Abdominal pain</td><td>16 (8.9)</td><td>6 (6.9)</td></tr>
<tr><td>Diarrhea</td><td>13 (7.2)</td><td>3 (3.4)</td></tr>
<tr><td>Abdominal distension</td><td>7 (3.9)</td><td>2 (2.3)</td></tr>
<tr><td>Flatulence</td><td>6 (3.3)</td><td>0</td></tr>
<tr><td>Nausea</td><td>6 (3.3)</td><td>1 (1.1)</td></tr>
</table>
</td>
<td>Author's Conclusion: Rebyota is a safe and effective treatment to reduce recurrent C. difficile infection following standard-of-care antibiotics with a sustained response through 6 months.

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</tr>
</table>

**From FDA review / analysis

FDA review of effectiveness summary[1]**:**
The primary efficacy analysis of the Phase 3 study 2017-01 (PUNCH CD3) met the second pre-specified statistical success threshold 0.9750 but did not meet the more stringent 0.9993 first specified success threshold.
Prior to the Applicant performing the analysis, FDA concluded that a posterior finding equivalent to meeting the first specified success threshold would be sufficient to demonstrate substantial evidence of effectiveness.
After the primary efficacy analysis only met the second specified success criteria, FDA considered whether the data from the study, as well as the data from the studies described in the Supportive Clinical Studies section below, would be sufficient to demonstrate substantial evidence of effectiveness.

In coming to their conclusion about substantial evidence of effectiveness, the review team took the following information into consideration:

1. the clinical context for recurrent CDI, which is a serious condition that can be associated with high morbidity and mortality;
2. the unmet medical need for recurrent CDI because treatment options are limited and can be complex and prolonged. Bezlotoxumab, indicated to reduce recurrence of CDI, requires intravenous infusion, and its usefulness in individuals with pre-existing congestive heart failure may be limited.
3. the challenges of enrolling placebo-controlled trials for FMT given availability of other FMT products under enforcement discretion;
4. the observed RBX2600 treatment success rate in the placebo-controlled study 2017-01 was similar to the treatment success rates reported from the open-label studies of REBYOTA and from randomized, placebo-controlled studies of other FMT products.

After presenting the data at the advisory meeting and receiving a positive recommendation from a substantial majority of committee members that the clinical data were adequate to support effectiveness of the product the review team concluded that the data submitted to the BLA demonstrate substantial evidence of effectiveness for the prevention of recurrent CDI in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

Clinical Studies	Study Design	RBX2600 (Rebyota) recipients	Placebo Recipients
2013-001^	Phase 2, open label, safety and effectiveness	34	N/A
2014-01 (PUNCH CD2)	Phase 2, double blind, RCT, placebo -controlled, safety and effectiveness	108	20
2015-01^	Phase 2, open label, safety and effectiveness	149	Historical control
2017-01 (PUNCH CD3)	Phase 3, double blind, RCT, placebo-controlled, safety and effectiveness	204	63
2019-01^ (ongoing)	Phase 3, open label, safety and tolerability	204	N/A
2019-02	Retrospective, safety, and tolerability	94	N/A

FDA review of Supportive Clinical Studies:

- The interpretation of these open-label data is limited due to lack of concurrent placebo control, inclusion of a different dosing regimen (2 doses) from what is intended for licensure (1 dose), and differences between study populations in the open-label and placebo-controlled studies.

Study 2013-001 (NCT01925417) was a Phase 2, multicenter, open-label, prospective, non-controlled study.

- Forty participants 18 years of age and older who had at least two recurrences after a primary episode or had at least two episodes of severe Clostridioides difficile-associated diarrhea resulting in hospitalization were enrolled in the study.
- Of the 40 enrolled participants, 34 received at least one treatment with REBYOTA.
- The primary efficacy endpoint was treatment success, defined as the absence of C. difficile associated diarrhea (passage of three or more unformed stools in 24 or fewer consecutive hours for at least two consecutive days) at 56 days after the last dose of REBYOTA treatment.
- Sixteen out of 32 participants who completed follow-up (50.0%) were considered a treatment success after the first treatment course with REBYOTA.

Study 2015-01 (NCT02589847) was a Phase 2, multicenter, open-label, prospective study to compare one dose REBYOTA with antibiotic-treated historical controls.

- Participants 18 years of age and older who had at least two recurrences after a primary 13 episode or had at least two episodes of severe CDI resulting in hospitalization were enrolled in the study.
- The primary efficacy endpoint was treatment success, measured by the recurrence-free rate of CDI diarrhea without the need for retreatment with C. difficile anti-infective therapy or fecal transplant through 56 days after completion of study treatment with REBYOTA.
- The efficacy analysis was performed on REBYOTA treated participants (n=142) who received at least one dose of REBYOTA, compared with a closely matched Historical Control arm (n=75) chosen from a retrospective chart review of participants treated with antibiotics for recurrent CDI who matched key eligibility criteria and had an evaluable treatment outcome.
- The proportion of participants with treatment success was higher in the REBYOTA arm (78.9%) as compared with the Historical Control arm (30.7%).

Study 2019-01 (NCT03931941) is an ongoing Phase 3, multicenter, open-label, prospective, non-controlled study to evaluate the safety and tolerability of REBYOTA for the prevention of recurrent CDI in participants who have had prior recurrent CDI that was resolved with antibiotic treatment.

- The primary efficacy endpoint is treatment success, defined as the absence of CDI through 8 weeks after treatment.
    - An ad hoc analysis of study 2019-01 effectiveness data available at the time of the cut-off date (April 20, 2021) showed that, at 8 weeks post REBYOTA treatment, 73.4% (113/154) of participants in the mITT population experienced treatment success.

Warnings, Precautions, and Adverse Effects[3]

Contraindication	Severe hypersensitivity (eg, anaphylaxis) to fecal microbiota (live) or any component of the formulation.
Warning / Precaution	• Hypersensitivity reactions: Ensure appropriate medical treatment is readily available in the event an acute anaphylactic reaction occurs following administration. • Food allergies: Because product is manufactured from human fecal matter, may contain food allergens; however, potential for the product to cause adverse reactions due to food allergens is unknown. • Transmissible infectious agents: Manufactured from human fecal matter; may carry risk of transmitting infectious agents. Infections thought to be transmitted by this product should be reported to the manufacturer.
Adverse Reactions	Gastrointestinal: Abdominal distention (4%), abdominal pain (9%), diarrhea (7%), flatulence (3%), nausea (3%)
Pregnancy considerations	Rectal administration is not expected to have systemic absorption; fetal exposure is not expected following maternal administration.
Breastfeeding considerations	Rectal administration is not expected to have systemic absorption; exposure via breast milk is not expected following maternal administration
Pediatric	Safety and Efficacy has not been established in patients younger than 18 years of age.
Hepatic / Renal dosing	There are no dosage adjustments provided in the manufacturer's labeling; however, not expected to be systemically absorbed.

Interactions[3]
There are no known significant interactions.

Dosage and Administration[3]

- Rectal: 150 mL (contents of 1 bag) as a single dose, administered 24 to 72 hours after completion of C. difficile treatment regimen.
- Prior to use, thaw completely by placing carton in refrigerator (2°C to 8°C [36°F to 46°F]) for ~24 hours; do not thaw using a heat source (eg, microwave, hot water).
- Administer via gravity flow using provided administration set; refer to manufacturer's product labeling for more information. Do not allow administration tube to sag or loop (may prevent entire dose from being delivered), do not squeeze the bag to deliver product (may cause patient discomfort), and do not hang bag from an IV stand. Some product will remain in tube after administration is complete. Dispose of all components in medical waste.

Monitoring Parameters[3]
None

Prepared by: Jenel Proksel, Pharm.D. BCPS.

Appendix: Summary of Safety Issues and Implications for Pharmacy Operations

Characteristic	Summary
Medication Information	
Drug generic name (brand name)	Fecal microbiota, (Rebyota)
Drug manufacturer	Ferring Pharmaceuticals, Inc.
Schedule of medication	None
Anticipated use per month, anticipated patient population	1-3
Route of administration	Rectal
Preparation	Prior to use, thaw completely by placing carton in refrigerator (2°C to 8°C [36°F to 46°F]) for ~24 hours; do not thaw using a heat source (eg, microwave, hot water). Do not refreeze after thawing; may be stored refrigerated at 2°C to 8°C (36°F to 46°F) and used within 5 days (including thaw time). Remove the bag containing thawed product from the outer carton and inner carton insert; do not remove product from the sealed outer bag. Presence of condensation is normal. Refer to manufacturer's product labeling for further instructions on attaching administration set.
Stability	
Recommended storage conditions for medication, and how to manage excursions outside these conditions	Upon receipt, store carton in an ultracold freezer (−60°C to −90°C [−76°F to −130°F]). Alternatively, may store refrigerated at 2°C to 8°C (36°F to 46°F) for up to 5 days (including thaw time); do not refreeze. Store administration set separately at 10°C to 34°C (50°F to 93°F); do not store in the freezer.
Does the manufacturer require patients to meet specific criteria for treatment with this medication? If so, where may healthcare providers find these criteria?	No
Operations Information	
Is filtration required during preparation or administration of the IV medication?	No ☐ Yes ☐ N/A ☒
Can medication doses be sent to patient care units via pneumatic tube system? See IC24.	No ☐ Yes ☐ N/A ☒
Does the manufacturer have a restricted or special distribution program? If so, how may healthcare providers contact the program?	No ☒ Yes ☐
Safety/Policy Information	
Will this impact a dynamic alternative alert?	No ☒ Yes ☐
Is the medication (brand name, generic name, product packaging) similar to any other medications on the Institute for Safe Medication Practices (ISMP) Sound-Alike-Look-Alike (SALA) list or confused names list? If not, is the medication expected to be added to the list? https://www.ismp.org/tools/tallmanletters.pdf http://www.ismp.org/Tools/confuseddrugnames.pdf	No ☒ Yes ☐
Does the product package insert currently have any black box warning? For what?	No ☒ Yes ☐
Is this medication a hazardous agent?	No ☒ Yes ☐
Is this medication classified as chemotherapy per AHFS 10:00?	No ☒ Yes ☐
Is the medication a vesicant or irritant?	No ☒ Yes ☐
Is this a high-alert medication that requires an indication? See MM02.	No ☒ Yes ☐

Are there contraindications or significant warnings against medication use?	No ☒ Yes ☐
Is special monitoring recommended when starting therapy with this medication (eg. Telemetry, BP, etc)?	No ☒ Yes ☐
Is there a Risk Evaluation and Management Strategy (REMS) program for the medication? If so, where may healthcare providers find these criteria?	No ☒ Yes ☐
Does the medication require precautions for disposal? What kind? See EC20 Disposal of Pharmaceutical Products; EC11 Chemo Drugs-Safety Precautions for Administration	No ☒ Yes ☐
Does this medication need to be considered for auto-wasting on the MAR or another avenue for documenting waste?	No ☒ Yes ☐
Will the medication be restricted: MS68 Levels of Care • To a specific level of care (LOC)? • To a specific location? • To specific services/ providers? • To providers credentialed in deep sedation or general anesthesia? • To patients who are on the medication prior to admit?	 No ☒ Yes ☐ Unknown ☐ No ☒ Yes ☐ Unknown ☐ No ☒ Yes ☐ Unknown ☐ No ☒ Yes ☐ Unknown ☐ No ☒ Yes ☐ Unknown ☐

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