NEW DRUG APPROVAL

Brand Name	Rebyota™
Generic Name	fecal microbiota, live - jslm
Drug Manufacturer	Ferring Pharmaceuticals Inc.

New Drug Approval

FDA approval date: November 30, 2022

Review designation: N/A

Type of review: N/A

Dispensing restriction: Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Clostridioides difficile (C. diff) is a germ (bacteria) that causes life-threatening diarrhea. It is usually a side-effect of taking antibiotics. C. diff can easily spread from person to person.

These infections mostly occur in:

- People 65 and older who take antibiotics and receive medical care.
- People staying in hospitals and nursing homes for a long period of time.
- People with weakened immune systems or previous infection with *C. diff.*

Symptoms include:

diarrhea: loose, watery stools (poop) for several days, fever, stomach tenderness, loss of appetite, nausea.

Clostridioides difficile infection (CDI) is one of the most common nosocomial infections and its morbidity and mortality is on the rise, particularly among hospitalized elderly patients. Colonization by the bacteria occurs via the fecal-oral route and infection is often facilitated by the disruption of normal intestinal flora.

More than 2.8 million antimicrobial-resistant infections occur in the U.S. each year, and more than 35,000 people die as a result. When *Clostridioides difficile*—a bacterium that is not typically resistant but can cause deadly diarrhea and is associated with antibiotic use—is added to these, the U.S. toll of all the threats in the report exceeds 3 million infections and 48,000 deaths.

Efficacy

The effectiveness of Rebyota™ was evaluated using a Bayesian analysis of data from a randomized, double-blind, placebo-controlled, multicenter Phase 3 study (Study 1), which formally integrated treatment success rates from a placebo-controlled Phase 2 study (Study 2). Enrolled adults in both studies were 18 years of age or older and had a confirmed diagnosis of recurrent CDI (one or more episodes in Study 1; two or more episodes in Study 2) which was defined as diarrhea (passage of 3 or more loose bowel movements within a 24-hour period for 2 consecutive days) and a positive stool test for C. difficile toxin or toxigenic C. difficile, or had at least two episodes of severe CDI resulting in hospitalization within the last year. Enrolled adults were required to have completed at least 10 consecutive days of antibiotic therapy and have their CDI under control (<3 unformed/loose, i.e., Bristol Stool Scale type 6-7, stools/day for 2 consecutive days). A minimum of 24 hours to a maximum of 72 hours (Study 1) or 24 hours to a maximum of 48 hours (Study 2) antibiotic washout period was required prior to administration of the assigned study treatment. In Study 1, enrolled adults were randomized 2:1 to a single dose of Rebyota™ or

placebo respectively. In Study 2, randomization was 1:1:1 to receive two doses of Rebyota™, two doses of placebo, or one dose of Rebyota™ and one dose of placebo, administered 7±2 days apart. Only data from the Rebyota™ one-dose group and the placebo group are described below and were integrated in the Bayesian analysis.

In the integrated efficacy analysis set, the demographic profile and baseline recurrent CDI characteristics of treated adults were similar in the Rebyota™ and placebo groups. In Study 1, a total of 262 adults were randomized and treated, of which 177 adults received Rebyota™ and 85 received placebo. Adults had a mean age of 60.1 years with 45.4% of adults 65 years of age or older, were mainly white (92.0%) and female (69.1%). In this study, 32.8% of adults received Rebyota™or placebo for their first recurrence of CDI. In Study 1, 87.4% of adults had received vancomycin alone prior to treatment. In Study 2, 39 adults received one dose of Rebyota™ and one dose of placebo and 43 adults received two doses of placebo. Adults in these two groups had a mean age of 59.8 years with 42.7% of adults 65 years of age or older, were mainly white (97.6%) and female (63.4%). In this study, 89.0% of adults had received vancomycin prior to treatment.

Treatment success was defined as the 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.

In the Bayesian analysis, the estimated rate of treatment success was significantly higher in the Rebyota™ group (70.6%) than in the Placebo group (57.5%) through 8 weeks after completing blinded treatment, resulting in a difference of 13.1 percentage points (95% Credible Interval: 2.3, 24.0) which corresponds to a 99.1% posterior probability that Rebyota™ is superior to Placebo.

Table 1: Efficacy Results: Treatment Success at 8 weeks post-Treatment (mITT Population*)

Parameter	Rebyota™ Mean (95% CrI)	Placebo Mean (95% CrI)	Treatment Effect (Rebyota™– Placebo) Mean (95% CrI)
Model-Estimated Treatment Success (%)	70.6 (64.1, 76.8)	57.5 (48.1, 67.1)	13.1 (2.3, 24.0)
Posterior Probability of Superiority	-	-	0.991[#]

CrI=credible interval

*mITT includes all randomized subjects excluding: 1) those who withdrew prior to treatment; 2) those in whom treatment was attempted but not completed; 3) those who discontinued from the study prior to evaluation of treatment outcome for the primary endpoint if the reason for exit was not related to CDI symptoms. [#]Pre-defined threshold was 0.975.

Study 1 evaluated sustained clinical response which was defined as treatment success at 8 weeks and no CDI event through 6 months after the last dose during the blinded period. The difference in sustained clinical response rate (9.1%; 95% CI: -3.6%, 21.7%) was not statistically significant between the Rebyota™ (65.5%) and the placebo groups (56.5%).

The most commonly reported (≥ 3%) adverse reactions occurring in adults following a single dose of Rebyota™ were abdominal pain, (8.9%), diarrhea (7.2%), abdominal distention (3.9%), flatulence (3.3%), and nausea (3.3%).

Safety

ADVERSE EVENTS

Across the 5 clinical studies, participants recorded solicited adverse events in a diary for the first 7 days after each dose of Rebyota™ or placebo. Participants were monitored for all other adverse events by queries during scheduled visits, with duration of follow-up ranging from 6 to 24 months after the last dose.

In an analysis of solicited and unsolicited adverse events reported in Study 1, the most common adverse reactions (defined as adverse events assessed as definitely, possibly, or probably related to Investigational Product by the investigator) reported by ≥3% of Rebyota™ recipients, and at a rate greater than that reported by placebo recipients, were abdominal pain, (8.9%), diarrhea (7.2%), abdominal distention (3.9%), flatulence (3.3%), and nausea (3.3%).

Table 2: Adverse Reactions* reported by ≥3% of Rebyota™ recipients, and at a rate greater than that reported by placebo recipients, within 8 weeks after receipt of Rebyota™ or placebo (Study 1).

Adverse Reaction	Rebyota™ N=180 n (%)	Placebo N=87 n (%)
Abdominal Pain	16 (8.9)	6 (6.9)
Diarrhea	13 (7.2)	3 (3.4)
Abdominal distension	7 (3.9)	2 (2.3)
Flatulence	6 (3.3)	0
Nausea	6 (3.3)	1 (1.1)

*Adverse reactions were defined as solicited and unsolicited adverse events that were assessed as definitely, possibly, or probably related to treatment by the study investigator

Most adverse reactions occurred during the first 2 weeks after treatment. After this, the proportion of patients with adverse reactions declined in subsequent 2-week intervals. Beyond 2 weeks after treatment only a few single adverse reactions were reported. Most adverse drug reactions were mild to moderate in severity. No life-threatening adverse reaction was reported.

Serious Adverse Reactions
In a pooled analysis of the 5 clinical studies, 10.1% (60/595) of Rebyota™ recipients (1 dose only) and 7.2% (6/83) of placebo recipients reported a serious adverse event within 6 months post last dose of investigational product. None of these events were considered related to the investigational product.

WARNINGS & PRECAUTIONS

Transmissible infectious agents
Because Rebyota™ is manufactured from human fecal matter it may carry a risk of transmitting infectious agents. Any infection suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Ferring Pharmaceuticals Inc.

Management of acute allergic reactions Appropriate medical treatment must be immediately available in the event an acute anaphylactic reaction occurs following administration of Rebyota™.

Potential presence of food allergens Rebyota™ is manufactured from human fecal matter and may contain food allergens. The potential for Rebyota™ to cause adverse reactions due to food allergens is unknown.

CONTRAINDICATIONS

Do not administer Rebyota™ to individuals with a history of a severe allergic reaction (e.g., anaphylaxis) to any of the known product components.

Clinical Pharmacology

MECHANISMS OF ACTION

The mechanism of action of Rebyota™ has not been established.

Dose & Administration

ADULTS

- Administer Rebyota™ 24 to 72 hours after the last dose of antibiotics for CDI.
- Administer a single dose of 150 mL rectally of Rebyota™

PEDIATRICS

N/A

GERIATRICS

N/A

RENAL IMPAIRMENT

N/A

HEPATIC IMPAIRMENT

N/A

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Suspension. A single dose is 150 Ml.