



Drug Coverage Policy

Effective Date.....8/1/2025

Coverage Policy Number.....IP0556

Policy Title.....Rebyota

Rebyota

- Rebyota (fecal microbiota, live-jslm – Ferring Pharmaceuticals Inc.)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

OVERVIEW

Rebyota is indicated for the prevention of recurrence of Clostridioides difficile infection (CDI) in patients \geq 18 years of age following antibiotic treatment for recurrent CDI. Limitation of use. Rebyota is not indicated for treatment of CDI.¹

Rebyota received fast track, orphan drug, and breakthrough therapy designations from the FDA.

Dosing/Administration

Rebyota is administered rectally as a single dose (150 mL) 24 to 72 hours after the last dose of antibiotics for CDI. Patients are instructed to empty their bladder and bowel (if possible) and lie in a left-side position or a knee-chest position. The tube tip from the Rebyota bag is inserted into the patient's rectum and Rebyota is delivered via gravity flow.¹

Rebyota and the administration set are shipped in a box; each box may contain up to six cartons of Rebyota and up to six administration sets.¹

Place in Therapy

Clostridioides difficile (formerly known as *Clostridium difficile*) is a spore-forming, gram-positive anaerobic bacillus that produces two exotoxins (toxin A and toxin B) and is a common cause of antibiotic-associated diarrhea.³ It is estimated *C. difficile* accounts for 15% to 25% of all episodes of antibiotic-associated diarrhea. The primary mode of transmission of *C. difficile* resulting in disease is person-to-person spread through the oral-fecal route, most commonly occurring in healthcare facilities. The main clinical symptoms of CDI include watery diarrhea, fever, loss of appetite, nausea, and abdominal pain/tenderness. However, symptoms of CDI range from mild diarrhea to severe cases including pseudomembranous colitis, toxic megacolon, perforations of the colon, sepsis, and rarely death. There are some patients who only have colonization with *C. difficile*. Although these patients test positive for the *C. difficile* organism or its toxin, they do not have disease caused by *C. difficile* and often do not have clinical symptoms of infection. Patients with infection exhibit clinical symptoms and test positive for the *C. difficile* organism or its toxin.

The estimated national burden of CDI was over 460,000 in 2017 (most current data available).⁴ Depending on the method of attribution, CDI is associated with 15,000 to 30,000 deaths in the US. Inpatient cost is estimated to exceed \$4.8 billion.⁵ Prevention of CDI, which includes infection control and antibiotic stewardship, is a national priority.⁴

Adults at higher risk for CDI include the elderly, patients receiving antibiotics (e.g., fluoroquinolones, third/fourth generation cephalosporins, clindamycin, carbapenems), those who underwent GI surgery or manipulations, those with long length of stay in healthcare settings, those with a serious underlying illness, and those with immunocompromising conditions.³ Risk factors in children are similar to those for adults.⁵

Recurrent CDIs are common and the risk of recurrence increases with each successive recurrence.⁵ Approximately 10% to 30% of patients who respond to antibiotic treatment for a first CDI will experience a second CDI (i.e., first recurrence). Of the patients with a resolved first recurrence, approximately 40% will experience a second recurrence. Subsequent recurrence rate of patients who have already had two or more recurrences is approximately 45% to 65%.⁶ Recurrent CDI contributes to increased risk of complications (e.g., intestinal perforation, megacolon, colectomy, sepsis) or death and increased healthcare utilization and cost.^{2,5} Furthermore, the 30-day mortality rate with recurrent CDI has been reported to be 11% for the first recurrence, 7% for second recurrences. Estimates suggest recurrent CDI is associated with a 33% increased risk of mortality at 180 days relative to patients who do not experience a recurrence.

Other Therapies: Fecal microbiota transplantation (FMT)

FMT is also known as stool transplantation; this is a method by which stool from a healthy donor is placed into another patient's GI tract to directly change the recipient's gut microbiota to normalize the composition.⁷ FDA finalized guidance regarding use of FMT for the treatment of CDI not responsive to standard therapies on November 29, 2022.⁸ FDA notes that stool banks (defined as an establishment that collects, prepares, and stores FMT products for distribution to other establishments, healthcare providers, or other entities for use in patient therapy or clinical research) should comply with the Investigational New Drug (IND) requirements. Compliance with IND requirements will help to ensure that stool donor and stool are appropriately screened and tested, and FMT processing adheres to appropriate current good manufacturing practice (cGMP). Establishments that collect or prepare FMT products solely under the direction of licensed healthcare providers for the purpose of treating their patients [e.g., a hospital laboratory] are not considered stool banks. FDA intends to exercise enforcement discretion with respect to IND requirements when the FMT product is not obtained from a stool bank; however, there are still certain recommendations.

The guidance does not apply when FMT is used for other purposes (i.e., treatment of conditions or diseases other than CDI).

There are different suppliers for FMT products; one of which is OpenBiome, based in Massachusetts.⁹ OpenBiome's FMT products are manufactured in accordance with cGMP regulations. Stool donors undergo regular and rigorous screenings for infectious agents and health risks; stool is tested for enteric pathogens and multi-drug-resistant organisms, including vancomycin resistant enterococci, methicillin-resistant *Staphylococcus aureus*, extended-spectrum beta-lactamases, and carbapenem-resistant Enterobacterales. Stool sample is mixed with a buffer to enable the bacteria to survive being frozen; products should be stored frozen or thaw prior to administration to a patient. OpenBiome offers two FMT formulations: a lower dose formulation for recurrent CDI that can be administered via upper delivery (nasoenteric/gastric tube or esophagogastroduodenoscopy) or lower delivery (colonoscopy, sigmoidoscopy, or enema) and a higher dose formulation for fulminant CDI for delivery via colonoscopy. Both formulations are 35 mL liquid preparations; the difference is the concentration. The recommended total volume for either treatment is 60 to 180 mL, inclusive of a saline flush for both cryobag and the scope. OpenBiome collects patient outcomes data at 8 weeks post FMT from physicians who use their products. Per their website, an overall cure rate of 79% has been observed in over 5,100 cases across over 1,100 facilities. The American Gastroenterological Association (AGA) National FMT Registry collects long-term effectiveness and safety outcomes from patients undergoing FMT. To date, the majority of patients (67%) in the registry received an FMT using OpenBiome material; other sources included hospital-based stool banks and patient-identified donors. At the 1-month check-in, CDI was resolved after FMT in 90% of patients (n = 200/222). Response to FMT was durable; of 112 patients who were cured at 1-month and attended the 6-month follow-up, 96% remained cured. Registry data also demonstrated that repeat FMT or subsequent antibiotic therapy could be used to achieve cure after failure of an initial FMT. Of the 11 patients who failed to respond to an initial FMT and were followed to 6 months, 86% had resolution after repeat FMT and 64% had resolution after use of metronidazole and/vancomycin.

Much of the current clinical experience with FMT comes from treatment of recurrent or refractory CDI and efficacy has been demonstrated.⁷ Cure rates as high as 90% have been reported, compared to success rates of 20% to 30% with prolonged antibiotic therapy. However, it is important to note that variability in clinical trials, including differences in CDI severity, donor screening, and FMT preparation, dose, and delivery, can affect the ability to generalize efficacy findings.⁹ FMT is included in guidelines as standard practice for the treatment of recurrent CDI.^{5,10} The routes of administration of fecal material vary and there are advantages and disadvantages associated with each route of administration.⁷ Current evidence is not strong enough to show one administration method is better than another and the appropriate method should depend on the individual clinical situation. FMT is being investigated for other infectious conditions (e.g., infectious gastroenteritis), autoimmune diseases (e.g., allergic disease, diabetes, IBD), general conditions (e.g., obesity, functional GI disorders), and behavior conditions (e.g., autism).

Minor AEs associated with FMT include abdominal discomfort, diarrhea, constipation, and low-grade fever; however possible complications of endoscopy and sedation should be taken into consideration.⁷ Furthermore, some patients may experience IBD flares after FMT. There may be a greater risk for infection following FMT in immunocompromised patients and the long-term immunologic effects are unknown.

Over the past few years, the FDA has issued several safety alerts regarding FMT. In June 2019, FDA alerted healthcare providers about the risk of transmission of bacterial infections caused by multi-resistant organisms; two immunocompromised patients developed invasive infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and one of the patients died.¹¹ In March 2020, there was another alert regarding the potential risk of serious or life-threatening

infections through use of FMT. It was suspected that infections caused by enteropathogenic *E. coli* (EPEC) and Shigatoxin-producing *E. coli* (STEC) occurred.¹²⁻¹⁴ Six patients developed such infections; four of whom required hospitalization and two patients died. However, upon further investigation, the FDA determined that for one of the two patients who died, it was unclear if the STEC infection contributed to their death and for the second patient, the FMT product tested negative for STEC and therefore, the STEC was not transmitted by the FMT product. More recently, the FDA issued safety alerts regarding the potential risk of transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease of 2019 (COVID-19) and monkeypox virus through FMT products.^{15,16}

Guidelines

IDSA/SHEA issued a focused update on the management of CDI in adults in 2021.¹⁰ For the treatment of a first CDI recurrence, Dificid is the preferred treatment option and oral vancomycin is an alternative. Zinplava is an adjunctive treatment option, given during administration of the antibiotic. Adjunctive use of Zinplava may also be considered in patients with a primary CDI episode and other risk factors for CDI recurrence (e.g., age \geq 65 years, history or use of immunosuppressive therapy, severe CDI on presentation). The panel notes that data shows that the addition of Zinplava reduced CDI recurrence after initial clinical cure at 12 weeks and reduced CDI-associated hospitalization at 30 days but there was no reduction in mortality (low certainty evidence). For the treatment of second and subsequent CDI recurrences, Dificid, oral vancomycin, and FMT are recommended; Zinplava can be used as adjunctive treatment.^{5,10} FMT should only be offered after appropriate antibiotic treatments for at least two CDI recurrences (i.e., three CDI episodes) have been tried. The panel cites anecdotal treatment success to up to 94% when FMT is administered via the small bowel and up to 100% when delivered via the colon.⁵ There are limited data on FMT administration in patients with severe, refractory CDI. FMT has been used in patients with underlying IBD, although it appears to be less effective in these patients compared with those without IBD; additionally, there are reports of IBD flares following FMT.

Recommendations from the American College of Gastroenterology (ACG) [2021] guidelines for the treatment/prevention of recurrent CDIs are similar to those from the IDSA/SHEA.¹⁷ Regarding use of FMT, ACG recommends FMT for patients with severe and fulminant CDI refractory to antibiotic therapy, particularly in patients who are poor surgical candidates. In patients who have had two or more recurrences, FMT (after SOC antibiotics) is recommended to prevent further recurrences. A single FMT resulted in cure in 66% to 91% of patients; multiple FMTs in short succession may be necessary for prolonged cure. Patients who do not want or cannot undergo repeat FMT, prolonged or indefinite treatment with vancomycin (i.e., long-term suppressive therapy) is an option. (Note that prolonged antibiotic therapy is not supported by the IDSA/SHEA). In critically ill patients, FMT may reduce CDI-related colectomy and sepsis and improve survival benefit. FMT can be considered in patients with recurrent CDI with underlying IBD. ACG cites analyses that showed reduced efficacy when FMT is delivered by enema compared with colonoscopic or capsule delivery. Zinplava is also noted as a consideration for the prevention of CDI recurrence in patients at high risk of recurrence. Guidelines from the American Society of Colon and Rectal Surgeons (ASCRS) [2021] recommend FMT for the third and subsequent CDI recurrences.¹⁸ National Comprehensive Cancer Network (NCCN) guidelines for prevention and treatment of cancer-related infections (version 1.2025 – June 20, 2025) note FMT should be considered for patients with relapsed/recurrent CDIs (except those with neutropenia).¹⁹ Zinplava can also be considered for patients with relapsed/recurrent episodes.

Coverage Policy

Rebyota is considered medically necessary when the individual meets ALL of the following criteria:

- 1. Prevention of recurrence of *Clostridioides difficile* infection (CDI).** Approve for 1 month if the patient meets **ALL** of the following (A, B, C, D and E):
 - A. Age 18 years or older
 - B. *Clostridioides difficile* infection (CDI) confirmed by positive stool test for the current episode
 - C. At least 2 recurrent CDI episodes (greater than or equal to 3 total CDI episodes)
 - D. Administration will occur 24-72 hours following completion of antibiotic course for CDI treatment
 - E. Medication is prescribed by or in consultation with an infectious disease or gastrointestinal specialist

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Rebyota for any other use is considered not medically necessary (criteria will be updated as new published data are available).

Coding Information

- 1) This list of codes may not be all-inclusive.
- 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

| CPT®* Codes | Description |
|-------------|--|
| 44705 | Preparation of fecal microbiota for instillation, including assessment of donor specimen |
| 0780T | Instillation of fecal microbiota suspension via rectal enema into lower gastrointestinal tract |

| HCPCS Codes | Description |
|-------------|---|
| C9399 | Unclassified drugs or biologicals (Code effective until 06/30/2023) |
| G0455 | Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen |
| J1440 | Fecal microbiota, live-jslm, 1 ml (Code effective 07/01/2023) |

| | |
|-------|--|
| J3490 | Unclassified drugs (Code effective until 06/30/2023) |
| J3590 | Unclassified biologics (Code effective until 06/30/2023) |

*Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.

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Revision Details

| Type of Revision | Summary of Changes | Date |
|-------------------|---|----------|
| Selected Revision | Prevention of recurrence of Clostridioides difficile infection (CDI). Updated positive stool test criteria with addition of “for current episode” and removed “within the previous 30 days”. Removed documentation requirements | 8/1/2025 |

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