Effective Date **5/1/2023**
Next Review Date… **5/1/2024**
Coverage Policy Number **IP0556**

Rebyota

Table of Contents

Related Coverage Resources

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. 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

This policy supports medical necessity review for Rebyota™ (fecal microbiota, live – jslm rectal suspension – Ferring).

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

Initial Approval Criteria

Rebyota is considered medically necessary for the prevention of recurrence of *Clostridioides difficile* infection (CDI) when the individual meets ALL of the following criteria:

1. Age 18 years or older
2. Documentation of *Clostridioides difficile* infection (CDI) confirmed by positive stool test within the previous 30 days
3. Documentation of at least 2 recurrent CDI episodes (greater than or equal to 3 total CDI episodes)

4. Administration will occur 24-72 hours following completion of antibiotic course for CDI treatment
5. 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.

Continuation of Therapy Criteria

Not applicable for continuation beyond initial approval duration.

Authorization Duration

Initial approval duration: 1 month
Reauthorization approval duration: not applicable

Conditions Not Covered

Any other use is considered experimental, investigational or unproven.

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.

Background

OVERVIEW
Rebyota is indicated for the prevention of recurrence of Clostridioides difficile infection (CDI) in patients ≥ 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 Enterobacterale. 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), automimmune 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 determmined 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 ≥ 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 2.2022 – August 19, 2022) 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.

References

1. Rebyota™ suspension for rectal use [prescribing information]. Parsippany, NJ: Ferring; November 2022.
2. Data on file. RBX2660™ Product Dossier. AMCP unapproved product dossier. Ferring. Received October 5, 2022.
3. Centers for Disease Control and Prevention. *Clostridioides difficile*. Available at: https://www.cdc.gov/cdiff/clinicians/faq.html. Accessed October 10, 2022.
4. Guh AY, Mu Y, Winston LG, et al. Trends in US burden of *Clostridioides difficile* infection and outcomes. *N Engl J Med*. 2020;382:1320-1330.
5. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018;66:e1-e48.
6. Song JH, Kim YS. Recurrent *Clostridium difficile* infection: risk factors, treatment, and prevention. *Gut and Liver*. 2019;13:16-24.
7. Wang JW, Kuo CH, Kuo FC, et al. Fecal microbiota transplantation: review and update. *J Formosan Med Assoc*. 2019;118:523-531.
8. Enforcement policy regarding investigational new drug requirements for use of fecal microbiota for transplantation to treat Clostridium difficile infection not responsive to standard therapies. Guidance for industry. Available at: https://www.idsociety.org/public-health/emerging-clinical-issues/emerging-clinical-issues/fecal-microbiota-transplantation. Accessed on December 12, 2022.
9. OpenBiome Website. Available at: https://openbiome.org/. Accessed on December 12, 2022.

10. Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. *Clin Inf Disease*. 2021;73:e1029-e1044.
11. FDA Alert. Fecal microbiota for transplantation: safety communication – risk of serious adverse reactions due to transmission of multi-drug resistant organisms. Posted on June 13, 2019. Available at: https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-safety-communication-risk-serious-adverse-reactions-due. Accessed on November 15, 2022.
12. FDA Alert. Fecal microbiota for transplantation: safety alert - risk of serious adverse events likely due to transmission of pathogenic organisms. Posted on March 12, 2020;. Available at: https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-safety-alert-risk-serious-adverse-events-likely-due-transmission. Accessed on November 15, 2022.
13. FDA Alert. Safety alert regarding use of fecal microbiota for transplantation and risk of serious adverse events likely due to transmission of pathogenic organisms. Posted on March 12, 2020. Available at: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse-events-likely. Accessed on November 15, 2022.
14. FDA Alert. Update to March 12, 2020 safety alert regarding use of fecal microbiota for transplantation and risk of serious adverse events likely due to transmission of pathogenic organisms. Posted on March 13, 2020. Available at: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/update-march-12-2020-safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious. Accessed on November 15, 2022.
15. FDA alert. Safety alert regarding use of fecal microbiota for transplantation and additional safety protections pertaining to SARS-CoV-2 and COVID 19. Posted on March 23, 2020. Available at: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-additional-safety-protections. Accessed on November 15, 2022.
16. FDA Alert. Safety alert regarding use of fecal microbiota for transplantation and additional safety protections pertaining to monkeypox virus. Posted on August 22, 2022. Available at: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-additional-safety-protections-0. Accessed on November 15, 2022.
17. Kelly CR, Fischer M, Allegretti JR, et al. American College of Gastroenterology (ACG) Clinical Guidelines: Prevention, diagnosis, and treatment of *Clostridioides difficile* infections. *Am J Gastroenterol*. 2021;116:1124-1147.
18. Poylin V, Hawkins AT, Bhama AR, et al. The American Society of Colon and Rectal Surgeons clinical practice guidelines for the management of *Clostridioides difficile* infection. *Dis Colon Rectum*. 2021;64:650-668.24.
19. The NCCN Prevention and Treatment of Cancer-Related Infections Clinical Practice Guidelines in Oncology (version 2.2022 – August 19, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 21, 2022.