

PHARMACY / MEDICAL – 5.01.631

Pharmacologic Treatment of Clostridioides Difficile

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RELATED MEDICAL POLICIES:

N/A

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Introduction

Clostridioides difficile infection (CDI) is a gram-positive, anaerobic, spore-forming bacillus that is responsible for the development of antibiotic-associated diarrhea and colitis. CDI occurs in about 500,000 individuals in the United States every year, with about half of the infections occurring in hospitalized individuals. There are a number of known risk factors for developing CDI. They include antibiotic exposure, gastrointestinal surgery, long stays in healthcare settings (including hospitals and nursing homes), immunocompromising conditions, and age over 65 years. This policy discusses when treatments for CDI may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
<ul style="list-style-type: none"> • Dificid (fidaxomicin) tablets/granules, oral • Fidaxomicin tablets, oral 	<p>Dificid (fidaxomicin) and fidaxomicin may be considered medically necessary when the following criteria are met:</p> <ul style="list-style-type: none"> • The individual is aged 6 months or older <p>AND</p> <ul style="list-style-type: none"> • Diagnosed with Clostridioides difficile (C. difficile) associated diarrhea <p>AND</p> <ul style="list-style-type: none"> • Meets 1 of the following: <ul style="list-style-type: none"> ○ Has tried and had an inadequate response or intolerance to generic oral metronidazole ○ Has tried and had an inadequate response or intolerance to generic oral vancomycin ○ There is documented C. difficile resistance to metronidazole AND documented C. difficile resistance to vancomycin <p>AND</p> <ul style="list-style-type: none"> • The dose is limited to 400 mg per day (taken as 200 mg twice a day) for 10 days
<p>Rebyota (fecal microbiota, live-jslm), rectal suspension</p>	<p>Rebyota (fecal microbiota, live-jslm) may be considered medically necessary when the following criteria are met:</p> <ul style="list-style-type: none"> • The individual is aged 18 years or older <p>AND</p> <ul style="list-style-type: none"> • Has had two or more recurrent Clostridioides difficile infection (CDI) episodes <p>AND</p> <ul style="list-style-type: none"> • Positive stool test for toxigenic Clostridioides difficile (C. difficile) within the last 30 days <p>AND</p> <ul style="list-style-type: none"> • Current episode of CDI is controlled defined as less than three loose stools per day for two consecutive days <p>AND</p> <ul style="list-style-type: none"> • Administration will occur within 72 hours following completion of antibacterial treatment for CDI <p>AND</p> <ul style="list-style-type: none"> • Rebyota (fecal microbiota, live-jslm) is limited to a single treatment course



Drug	Medical Necessity
<p>Vowst (fecal microbiota spores, live-brpk) capsules, oral</p>	<p>Vowst (fecal microbiota spores, live-brpk) may be considered medically necessary when the following criteria are met:</p> <ul style="list-style-type: none"> • The individual is aged 18 years or older <p>AND</p> <ul style="list-style-type: none"> • Has had two or more recurrent Clostridioides difficile infection (CDI) episodes <p>AND</p> <ul style="list-style-type: none"> • Positive stool test for toxigenic Clostridioides difficile (C. difficile) within the last 30 days <p>AND</p> <ul style="list-style-type: none"> • Current episode of CDI is controlled defined as less than three loose stools per day for two consecutive days <p>AND</p> <ul style="list-style-type: none"> • Administration will occur within 72 hours following completion of antibacterial treatment for CDI <p>AND</p> <ul style="list-style-type: none"> • Vowst (fecal microbiota spores, live-brpk) is limited to a single treatment course
<p>Zinplava (bezlotoxumab), IV</p>	<p>Zinplava (bezlotoxumab) may be considered medically necessary when the following criteria are met:</p> <ul style="list-style-type: none"> • The individual is aged 1 year or older <p>AND</p> <ul style="list-style-type: none"> • Has a diagnosis of Clostridioides difficile infection (CDI) confirmed by a positive stool test for toxigenic Clostridioides difficile (C. difficile) <p>AND</p> <ul style="list-style-type: none"> • Is at high risk for CDI recurrence due to one of the following: <ul style="list-style-type: none"> ○ Is 65 years or older <p>OR</p> <ul style="list-style-type: none"> ○ Is immunocompromised <p>OR</p> <ul style="list-style-type: none"> ○ Severe CDI at presentation <p>OR</p> <ul style="list-style-type: none"> ○ Presence of C. difficile ribotype 027 <p>AND</p> <ul style="list-style-type: none"> • Is currently receiving standard of care antibacterial therapy for CDI (e.g., fidaxomicin, metronidazole, or vancomycin)



Drug	Medical Necessity
	<p>AND</p> <ul style="list-style-type: none"> Zinplava (bezlotoxumab) is limited to a single treatment course

Drug	Investigational
<p>Dificid (fidaxomicin), fidaxomicin, Rebyota (fecal microbiota, live-jslm), Vowst (fecal microbiota spores, live-brpk), Zinplava (bezlotoxumab) IV</p>	<p>All other uses of Dificid (fidaxomicin), fidaxomicin, Rebyota (fecal microbiota, live-jslm), Vowst (fecal microbiota spores, live-brpk) and Zinplava (bezlotoxumab) for conditions not outlined in this policy are considered investigational.</p> <p>The medications listed in this policy are subject to the product’s US Food and Drug Administration (FDA) dosage and administration prescribing information.</p>

Length of Approval	
Approval	Criteria
<p>Initial authorization</p>	<p>Non-formulary exception reviews for Dificid (fidaxomicin), fidaxomicin, Rebyota (fecal microbiota, live-jslm), Vowst (fecal microbiota spores, live-brpk) and Zinplava (bezlotoxumab) may be approved up to 12 months.</p> <p>All other reviews for Dificid (fidaxomicin), fidaxomicin, Rebyota (fecal microbiota, live-jslm), Vowst (fecal microbiota spores, live-brpk) and Zinplava (bezlotoxumab) may be approved up to 1 month.</p>
<p>Re-authorization criteria</p>	<p>Future re-authorization of Dificid (fidaxomicin) and fidaxomicin for the treatment of C. difficile associated diarrhea will be reviewed as an initial request.</p> <p>Future re-authorization of Rebyota (fecal microbiota, live-jslm) and Vowst (fecal microbiota spores, live-brpk) following the administration of one treatment course is considered investigational.</p> <p>Future re-authorization of Zinplava (bezlotoxumab) following the administration of one dose is considered investigational.</p>



Documentation Requirements

The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

Coding

Code	Description
CPT	
0780T	Instillation of fecal microbiota suspension via rectal enema into lower gastrointestinal tract
Code	Description
HCPCS	
J0565	Injection, bezlotoxumab (Zinplava), 10 mg
J1440	Fecal microbiota, live – jslm (Rebyota), 1 ml
J3590	Unclassified biologics (use to report: Vowst)

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Related Information

Benefit Application

Rebyota (fecal microbiota, live-jslm) is managed through the pharmacy and medical benefit. Dificid (fidaxomicin), fidaxomicin, and Vowst (fecal microbiota spores, live-brpk) are managed through the pharmacy benefit. Zinplava (bezlotoxumab) is managed through the medical benefit.



Clinical Trials

Rebyota was evaluated in the Phase 3 PUNCH CD3 clinical trial (NCT03244644) in individuals with at least one recurrence after a primary episode of CDI or those who have had at least two episodes of severe CDI resulting in hospitalization within the past year. The primary endpoint was absence of *C. difficile* diarrhea without the need for retreatment as assessed by subject interview and physical examination at 8 weeks. Rebyota demonstrated superior efficacy compared with placebo (70.4% and 58.1%, respectively). Safety in the Rebyota arm was comparable to placebo. To evaluate the effectiveness of Rebyota, a Bayesian model was used in which certain results from a placebo-controlled Phase 2 study (PUNCH CD2, NCT02299570) were integrated into the PUNCH CD3 results. All individuals in both trials had a diagnosis of recurrent CDI, although the number of required recurrences differed between trials. The definition of recurrent CDI included diarrhea (passage of three or more loose bowel movements within a 24-hour period for 2 consecutive days) with a positive stool test for *C. difficile* toxin or toxigenic *C. difficile*, or at least two episodes of severe CDI resulting in hospitalization within the last year. All enrolled individuals had completed at least 10 consecutive days of antibiotic therapy. In PUNCH CD3, 87% of individuals had been treated with vancomycin alone. 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.

The efficacy and safety of Vowst was studied in a phase III, randomized, placebo-controlled, multi-center study. The primary efficacy endpoint was to see if there was reduction of CDI recurrence with the Vowst treatment. The study included 182 adult individuals with confirmed diagnosis of recurrent CDI (with a total of at least 3 episodes of CDI within 12 months) were randomized 1:1 to receive a dose of Vowst (n = 89) or placebo (n = 93) once daily for 3 consecutive days. One day before starting the assigned treatment regimen, individuals were required to have bowel cleansing using either magnesium citrate or polyethylene glycol electrolyte solution.

The primary efficacy endpoint was CDI recurrence through 8 weeks after completion of treatment. The CDI recurrence was measured through 3 or more unformed stools per day for 2 consecutive days with continued diarrhea until antibacterial treatment was initiated, or a positive *C. difficile* test on a stool sample determined by a toxin assay.

At the end of the week 4, 11.2% in the treatment group and 33.3 % in the placebo group (p-value < 0.001) experienced CDI recurrence. Similarly, at the end of the week 8, 12.4% in the



treatment group and 39.8% in the placebo group (p-value < 0.001) experienced CDI recurrence. These statistically significant benefits were maintained through 24 weeks of follow-up.

In the Vowst group, no serious adverse events were observed. Most frequently reported adverse events were GI disorders (abdominal distension, fatigue, constipation, chills and diarrhea).

References

1. Rebyota (fecal microbiota, live-jslm) prescribing information. Merck Sharp & Dohme Corp. Rahway, NJ. Revised November 2022.
2. Zinplava (bezlotoxumab) prescribing information. Ferring Pharmaceuticals Inc. Saint-Prex, Switzerland. Revised May 2023.
3. Centers for Disease Control and Prevention. FAQs for clinicians about C. diff. March 5, 2024. <https://www.cdc.gov/c-diff/hcp/clinical-overview/index.html> Accessed March 11, 2025.
4. Centers for Disease Control and Prevention. Nearly half a million Americans suffered from Clostridium difficile infections in a single year. March 22, 2017. https://archive.cdc.gov/www_cdc_gov/media/releases/2015/p0225-clostridium-difficile.html Accessed March 11, 2025.
5. Dubberke ER, et al. Results from a randomized, placebo-controlled clinical trial of a RBX2660- a microbiota-based drug for the prevention of recurrent Clostridium difficile Infection. *Clin Infect Dis*. 2018;67(8):1198–1204. doi:10.1093/cid/ciy259
6. Gough E, et al. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. *Clin Infect Dis*. 2011;53(10):994– 1002. doi:10.1093/cid/cir632
7. Guh AY, et al. Trends in U.S. burden of Clostridioides difficile infection and outcomes. *New Engl J Med*. 2020;382:1320–1330. doi:10.1056/NEJMoa1910215
8. Gupta S, et al. Fecal microbiota transplantation: in perspective. *Therap Adv Gastroenterol*. 2016;9(2):229–239. doi:10.1177/1756283X15607414
9. Khanna S, et al. Efficacy and safety of RBX2660 in PUNCH CD3, a phase III, randomized, double-blind, placebo-controlled trial with a Bayesian primary analysis for the prevention of recurrent Clostridioides difficile infection [published correction appears in *Drugs*. 2022]. *Drugs*. 2022;82(15):1527–1538. doi:10.1007/s40265-022-01797-x
10. Kwak S, et al. Impact of investigational microbiota therapeutic RBX2660 on the gut microbiome and resistome revealed by a placebo-controlled clinical trial. *Microbiome*. 2020;8(1):125. doi:10.1186/s40168-020-00907-9
11. Langdon A, et al. Microbiota restoration reduces antibiotic-resistant bacteria gut colonization in patients with recurrent Clostridioides difficile infection from the open-label PUNCH CD study. *Genome Med*. 2021;13(1):28. doi:10.1186/s13073-021-00843-9
12. Moayyedi P, et al. Canadian Association of Gastroenterology position statement: fecal microbiota transplant therapy. *Can J Gastroenterol Hepatol*. 2014;28(2):66–68. doi:10.1155/2014/346590
13. Orenstein R, et al. Durable reduction of Clostridioides difficile infection recurrence and microbiome restoration after treatment with RBX2660: results from an open-label phase 2 clinical trial. *BMC Infect Dis*. 2022;22(1):245. doi:10.1186/s12879-022-07256-y
14. Orenstein R, et al. Safety and durability of RBX2660 (microbiota suspension) for recurrent Clostridium difficile infection: Results of the PUNCH CD Study. *Clin Infect Dis*. 2016;62(5):596–602. doi:10.1093/cid/civ938



15. Rohlke F, Stollman N. Fecal microbiota transplantation in relapsing *Clostridium difficile* infection. *Therap Adv Gastroenterol*. 2012;5(6):403–420. doi:10.1177/1756283X12453637
16. Song JH, et al. Recurrent *Clostridium difficile* infection: risk factors, treatment and prevention. *Gut Liver*. 2019;13(1):16–24. doi: 10.5009/gnl18071
17. Suzuki R, et al. Contact urticaria syndrome and protein contact dermatitis caused by glycerin enema. *JAAD Case Rep*. 2016;2(2):108–110. doi: 10.1016/j.jdcr.2015.12.011
18. U.S. Food and Drug Administration. FDA Approves First Orally Administered Fecal Microbiota Product for the Prevention of Recurrence of *Clostridioides difficile* Infection. April 26, 2023. <https://www.fda.gov/news-events/press-announcements/fda-approves-first-orally-administered-fecal-microbiota-product-prevention-recurrence-clostridioides> Accessed March 11, 2025.
19. U.S. Food and Drug Administration. Important safety alert regarding use of fecal microbiota for transplantation and risk of serious adverse reactions due to transmission of multi-drug resistant organisms. Updated March 12, 2020. <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse-events-likely> Accessed March 11, 2025.
20. U.S. Food and Drug Administration. Safety alert regarding use of fecal microbiota for transplantation and additional safety protections pertaining to monkeypox virus. August 22, 2022. <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-additional-safety-protections-0> Accessed March 11, 2025.
21. U.S. Food and Drug Administration. Safety alert regarding use of fecal microbiota for transplantation and additional safety protections pertaining to SARS-CoV-2 and COVID-19. March 23, 2020. <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-additional-safety-protections> Accessed February 24, 2026.
22. U.S. Food and Drug Administration. 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. March 13, 2020. <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 February 24, 2026.
23. van Nood E, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med*. 2013;368(5):407–415. doi:10.1056/NEJMoa1205037
24. Vowst (fecal microbiota spores, live-brpk) Prescribing Information. Aimmune Therapeutics, Inc. Brisbane, CA. Revised February 2025.
25. Difidid (fidaxomicin) Prescribing Information. Merck Sharp & Dohme LLC, Rahway, NJ. Revised June 2022.
26. Lisa M, et al. ECOSPOR III - SER-109 Versus Placebo in the Treatment of Adults With Recurrent *Clostridium Difficile* Infection (ECOSPORIII). Available at: ECOSPOR III - SER-109 Versus Placebo in the Treatment of Adults With Recurrent *Clostridium Difficile* Infection - Full Text View - ClinicalTrials.gov. Accessed on March 11, 2025.
27. Elaine W, et al. ECOSPOR IV: An Open-Label Study Evaluating SER-109 in Recurrent *Clostridioides Difficile* Infection. Available at: ECOSPOR IV: An Open-Label Study Evaluating SER-109 in Recurrent *Clostridioides Difficile* Infection - Full Text View - ClinicalTrials.gov. Accessed on March 11, 2025.
28. Feuerstadt P, Chopra T, Knappe W, et al. PUNCH CD3-OLS: a phase 3 prospective observational cohort study to evaluate the safety and efficacy of fecal microbiota, live-jslm (REBYOTA) in adults with recurrent *Clostridioides difficile* infection. *Clin Infect Dis*. Aug 24 2024. PMID 39180326

History



Date	Comments
04/01/23	New policy, approved March 14, 2023, effective for dates of service on or after July 6, 2023. Added Rebyota (fecal microbiota, live-jslm) and Zinplava (bezlotoxumab) coverage criteria. Added HCPC code Zinplava and code J3590 for Rebyota.
07/01/23	Coding update. Added new HCPCS code J1440.
08/01/23	Interim Review, approved July 11, 2023. Added Vowst (fecal microbiota spores, live-brbk) coverage criteria. Added Vowst to HCPCS code J1440.
01/01/24	Coding update and coding correction. Vowst removed from HCPCS code J1440 and added to HCPCS code J3590.
09/01/24	Annual Review, approved August 12, 2024. No changes to policy statements.
04/01/25	Annual Review, approved March 24, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.
09/01/25	Interim Review, approved August 12, 2025. Added coverage for Dificid (fidaxomicin) for the treatment of C. difficile associated diarrhea.
10/01/25	Coding update. Added CPT code 0780T for the administration of Rebyota.
04/01/26	Annual Review, approved March 10, 2026. Added fidaxomicin to the policy with same criteria as Dificid (fidaxomicin). Updated Zinplava (bezlotoxumab) age requirement from aged 18 years or older to aged 1 year or older.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2026 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

