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PHARMACY – 5.01.631

Pharmacologic Treatment of Clostridioides Difficile

BCBSA Ref. Policy: 2.01.92

Effective Date:	Apr. 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Mar. 24, 2025	N/A
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∞ Clicking this icon returns you to the hyperlinks menu above.

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
Rebyota (fecal microbiota, live-jslm) rectal suspension	**Rebyota (fecal microbiota, live-jslm) may be considered medically necessary when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has had two or more recurrent Clostridioides difficile infection (CDI) episodes **AND** • Positive stool test for toxigenic Clostridioides difficile (C. difficile) within the last 30 days **AND** • Current episode of CDI is controlled defined as less than three loose stools per day for two consecutive days **AND** • Administration will occur within 72 hours following completion of antibacterial treatment for CDI **AND** • Rebyota (fecal microbiota, live-jslm) is limited to a single treatment course
Vowst (fecal microbiota spores, live-brpk) capsules, for oral administration	**Vowst (fecal microbiota spores, live-brpk) may be considered medically necessary when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has had two or more recurrent Clostridioides difficile infection (CDI) episodes **AND** • Positive stool test for toxigenic Clostridioides difficile (C. difficile) within the last 30 days **AND** • Current episode of CDI is controlled defined as less than three loose stools per day for two consecutive days **AND** • Administration will occur within 72 hours following completion of antibacterial treatment for CDI **AND** • Vowst (fecal microbiota spores, live-brpk) is limited to a single treatment course

Drug	Medical Necessity
Zinplava (bezlotoxumab) IV	**Zinplava (bezlotoxumab) may be considered medically necessary when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has a diagnosis of Clostridioides difficile infection (CDI) confirmed by a positive stool test for toxigenic Clostridioides difficile (C. difficile) **AND** • Is at high risk for CDI recurrence due to one of the following: ○ Is 65 years or older **OR** ○ Is immunocompromised **OR** ○ Severe CDI at presentation **OR** ○ Presence of C. difficile ribotype 027 **AND** • Is currently receiving standard of care antibacterial therapy for CDI (e.g., fidaxomicin, metronidazole, or vancomycin) **AND** • Zinplava (bezlotoxumab) is limited to a single treatment course

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

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for Rebyota (fecal microbiota, live-jslm), Vowst (fecal microbiota spores, live-brpk) and Zinplava (bezlotoxumab) may be approved up to 12 month.** **All other reviews for Rebyota (fecal microbiota, live-jslm), Vowst (fecal microbiota spores, live-brpk) and Zinplava (bezlotoxumab) may be approved up to 1 month.**
Re-authorization criteria	**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.** **Future re-authorization of Zinplava (bezlotoxumab) following the administration of one dose is considered investigational.**

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
HCPCS	
J0565	Injection, bezlotoxumab (Zinplava), 10 mg
J1440	Fecal microbiota, live – jslm (Rebyota), 1 ml
J3590	Unclassified biologics (use to report: Vowst)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Benefit Application

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

Evidence Review

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 ≥ 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

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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.

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). ©2025 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.