Medical Benefit Drug Policy

Rebyota (fecal microbiota, live - jslm) suspension, for rectal use

Policy Number: MC/PC 034
Effective Date: May 1, 2025

Instructions for Use

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Related Policies

- n/a

Coverage Rationale

Recurrent *Clostridioides difficile* infection (CDI)

For initial coverage of Rebyota for recurrent *Clostridioides difficile* infection (CDI), the following will be required:

- Patient is 18 years of age or older **and**
- Patient has a history of one or more recurrent episodes of CDI **and**
- Diagnosis of recurrent *clostridioides difficile* infection (CDI) as defined by both of the following:
  - Presence of diarrhea defined as a passage of 3 or more loose bowel movements within a 24-hour period for 2 consecutive days
  - A positive stool test for *C.difficile* toxin or toxigenic *C.difficile* **and**
- Both of the following:
  - Patient has completed at least 10 consecutive days of one of the following antibiotic therapies between 24 to 72 hours prior to initiating Rebyota:
    - oral vancomycin
    - Dificid (fidaxomicin) **and**
  - Previous episode of CDI is under control (e.g., less than 3 unformed/loose [i.e., Bristol Stool Scale type 6-7] stools/day for 2 consecutive days) **and**
- Prescribed by or in consultation with one of the following:
  - Gastroenterologist
  - Infectious disease specialist

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-

covered health service. Benefit coverage for health services is determined by t
document and applicable laws that may require coverage for a specific service
any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J1440	Fecal microbiota, live – jslm, 1 mL
G0455	Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen

ICD-10 Code	Description
A04.71	Enterocolitis due to Clostridium difficile, recurrent

Background

Clostridioides (formerly Clostridium) difficile is a spore-forming, anaerobic, gram-positive bacillus (rod) which causes diarrhea and colitis that can potentially be life-threatening and is considered an urgent threat by the Centers for Disease Control and Prevention (CDC) (CDC 2019, CDC 2021). C. difficile accounts for 15 to 25% of all antibiotic-associated diarrhea (AAD) episodes in the United States (U.S.) and is associated with significant morbidity and mortality, accounting for 15,000 to 30,000 deaths annually (CDC 2021, Fu et al 2021). C. difficile infection (CDI) is spread through person-to-person contact via the fecal-oral route, or from direct exposure to an environment contaminated with C. difficile spores (CDC 2021).

Clinical Evidence

Rebyota was evaluated using a Bayesian analysis of data from the Phase 3, randomized, double-blind (DB), placebo-controlled (PC), multi-center (MC) PUNCH CD3 trial, which integrated treatment success rates from the Phase 2 randomized, DB, PC, MC PUNCH CD2 trial (Dubberke et al 2018, Khanna et al 2022). Both studies enrolled patients ≥ 18 years of age, with a confirmed diagnosis of rCDI (≥ 1 episode in PUNCH CD3 and ≥ 2 episodes in PUNCH CD2) or had ≥ 2 episodes of severe CDI resulting in hospitalization in the last year. The overall patient population was White, and patients with inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), or immunocompromised disease states were excluded, limiting the applicability of these results to a more diverse population. Enrolled patients were required to have completed ≥ 10 consecutive days of standard of care (SOC) anti-CDI antibiotics (e.g., vancomycin, fidaxomicin, or metronidazole) and have their CDI under control (< 3 unformed/loose stools for 2 consecutive days). A minimum of a 24-to-72-hour washout antibiotic period was required prior to administration of the assigned study treatment.

In PUNCH CD2, randomization was 1:1:1 to receive 2 doses of Rebyota, 2 doses of placebo, or 1 dose of Rebyota and 1 dose of placebo administered 7 ± 2 days apart. In PUNCH CD3, randomization was 2:1 to a single dose of Rebyota or placebo, respectively. Only results from patients receiving 1 dose of Rebyota and placebo were integrated into the Bayesian analysis, as patients receiving 2 doses of Rebyota failed to demonstrate superiority in prevention of rCDI vs placebo in PUNCH CD2. In the integrated efficacy analysis set, baseline characteristics were similar in the Rebyota and placebo groups. Treatment success was defined as absence of CDI diarrhea within 8 weeks of blinded treatment. The estimated rate of treatment success was significantly higher in the Rebyota group (70.6%) vs placebo (57.5%) resulting in a difference of 13.1% (95% credible interval [CrI], 2.3 to 24.0), which corresponded to a 99.1% posterior probability that Rebyota was superior to placebo, exceeding the 97.5% threshold selected to control for type 1 error. Both PUNCH CD2 and PUNCH CD3 allowed patients to receive an open-label (OL) dose of Rebyota after the study treatment was completed. This led to 80 to 89% of patients who received ≥ 1 dose (median, 2 doses) of Rebyota achieving treatment success (i.e., no recurrence of CDI diarrhea within 8 weeks of receipt of last dose of Rebyota). An ongoing safety and efficacy analysis is being conducted in an OL study (PUNCH CD3-OLS) (Clinicaltrials.gov Web site).

Place in therapy
Rebyota (rectal enema) and Vowst (oral capsule) are microbiota-based live biotherapeutic drugs approved for the prevention of rCDI in adult patients after completion of SOC antibiotics for treatment of CDI. Guidelines have not yet established recommendations regarding Rebyota or Vowst.

Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)
The IDSA-SHEA guidelines contain numerous treatment options for individuals with multiple (i.e., two or more) recurrences of CDI. In addition, fecal microbiota transplantation (FMT) is an option for those with multiple recurrences. It is recommended that FMT be reserved for individuals who have established proper antibiotic treatment for at least two episodes of recurrence (or three CDI episodes). This is because of the potential for adverse events such as the transmission of pathogenic organisms, including Escherichia coli and severe acute respiratory syndrome coronavirus 2 (Johnson et al., 2021).

American College of Gastroenterology (ACG)
The 2021 ACG guidelines suggest FMT be considered for individuals with severe and fulminant CDI refractory to antibiotic therapy, predominantly when they are poor surgical candidates (strong recommendation, low quality of evidence) (Kelly et al., 2021). The ACG recommends FMT to avoid further recurrence in individuals with a second or more CDI recurrence (strong recommendation, moderate quality of evidence). The endorsed delivery method is through colonoscopy or capsules for treating rCDI (strong recommendation, moderate quality of evidence). The ACG suggests enema delivery only if other methods are unavailable (conditional recommendation, low quality of evidence). Repeat FMT is recommended for individuals with a CDI recurrence within eight weeks of the first FMT (conditional recommendation, very low quality of evidence). FMT should be considered for rCDI individuals with IBD (strong recommendation, very low quality of evidence).

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID)
In 2021, the ESCMID updated its recommendations on the treatment guidance document for Clostridioides difficile infection in adults (van Prehn et al., 2021). The ESCMID suggests FMT may be a rescue therapy for individuals with severely complex CDI that has declined despite CDI antibiotic treatment and for whom surgery is not an option (Weak, Very Low). The ESCMID notes that evidence has shown that FMT has become an acknowledged treatment for multiple recurrent CDI as experience with FMT rises; it has become clear that there might be a role for FMT in severe complicated refractory CDI. The ESCMID recommends treatment opportunities for a second or further CDI recurrence consisting of FMT after SoC antibiotic pre-treatment or bezlotoxumab in addition to standard of care antibiotic treatment; either depends on individual characteristics, earlier treatment, local regulations, obtainability, and practicability. For FMT, a suitable multidisciplinary risk assessment is needed, and FMT products should be obtainable with standardized preparation and screening (Weak, Moderate [FMT] /Low [bezlotoxumab]).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Rebyota is indicated for the prevention of recurrence of Clostridioides difficile infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

Limitation of Use: Rebyota is not indicated for treatment of CDI.

References

1. Centers for Disease Control and Prevention (CDC). Antibiotic resistance threats in the United States. 2019. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf Accessed September 9, 2024.
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Policy History/Revision Information

Date	Summary of Changes
4/16/2025	Approved by OptumRx P&T Committee

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. The insurance reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

OptumRx may also use tools developed by third parties to assist us in administering health benefits. OptumRx Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Archived Policy Versions (Internal Only)

Effective Date	Policy Number	Policy Title
mm/dd/yyyy – mm/dd/yyyy	######	Title of Policy Hyperlinked to KL or Other Internal Location

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Aspirus Health Plan, Inc.:
Provides people with disabilities reasonable modifications and free appropriate auxiliary aids and services to communicate effectively with us, such as:

- Qualified sign language interpreters.
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Provides free language assistance services to people whose primary language is not English, which may include:

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Southampton, PA 18966-9998
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Fax: 763-847-4010
Email: customerservice@aspirushealthplan.com

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U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1.800.368.1019, 800.537.7697 (TDD)

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