Fecal microbiota, live-jslm (Rebyota™)

Policy # 00852
Original Effective Date: 10/09/2023
Current Effective Date: 10/09/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider fecal microbiota, live-jslm (Rebyota™)‡ for the prevention of recurrence of *Clostridioides difficile* infection to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for fecal microbiota, live-jslm (Rebyota) will be considered when the following criteria are met:

- Rebyota is being requested for the prevention of recurrence of *Clostridioides difficile* infection (CDI); AND
- Rebyota is NOT being requested for the treatment of CDI; AND
- Patient is 18 years of age or older; AND
- Patient has had at least 2 or more recurrences of CDI infection that have been treated with antibiotics; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Current episode of CDI has been verified with a positive stool test for *Clostridioides difficile* toxin; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Administration of Rebyota will occur 24 to 72 hours after the last dose of antibiotic treatment; AND

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- There is clinical evidence or patient history that suggests the use of bezlotoxumab (Zinplava™)‡ will be ineffective or cause an adverse reaction to the patient.
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of fecal microbiota, live-jslm (Rebyota) when the ANY of following criteria are NOT met to be **not medically necessary**:**

- Patient has had at least 2 or more recurrences of CDI infection that have been treated with antibiotics
- Current episode of CDI has been verified with a positive stool test for *Clostridioides difficile* toxin
- There is clinical evidence or patient history that suggests the use of bezlotoxumab (Zinplava) will be ineffective or cause an adverse reaction to the patient

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers fecal microbiota, live-jslm (Rebyota) for any indication other than the prevention of recurrence of CDI to be **investigational.***

Based on review of available data, the Company considers fecal microbiota, live-jslm (Rebyota) when the patient selection criteria are not met (EXCEPT those denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Rebyota is indicated for the prevention of recurrence of *Clostridioides difficile* infection (CDI) in patients greater than or equal to 18 years of age following antibiotic treatment for recurrent CDI. It is not indicated for CDI treatment. Rebyota is available as a 150 ml suspension that contains fecal microbiota manufactured from human fecal matter sourced from qualified donors. It is administered rectally and should be give 24 to 72 hours after the last dose of antibiotic therapy.

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***Clostridioides difficile* Infection**
Clostridioides difficile is an anaerobic gram positive, spore forming, toxin-producing bacillus that is transmitted through the oral-fecal route. This pathogen is commonly found in healthcare facilities. Symptoms of CDI include abdominal pain or tenderness, watery diarrhea, fever, loss of appetite, and nausea. More severe cases of CDI often include pseudomembranous colitis, toxic megacolon, perforations of the colon, sepsis, and death, which is rarer than those previously mentioned. Recurrent CDIs are common, and the risk of recurrence increases with each successive recurrence. Risk of complications also increases with recurrent CDI. Examples of complications with recurrent CDI include, but are not limited to, intestinal perforation, megacolon, colectomy, sepsis, and death. Recommended treatment for recurrent CDI includes Dificid®‡ (fidaxomicin) and oral vancomycin for first recurrences with bezlotoxumab (Zinplava) being an adjunctive agent and Dificid, oral vancomycin, or fecal microbiota transplantation (FMT) for second and subsequent recurrences, with Zinplava again being recommended as an adjunctive agent. Rebyota is the first FDA approved fecal microbiota therapy to treat recurrent CDI.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Rebyota was approved in November of 2022 for the prevention of recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The effectiveness of Rebyota was evaluated using a Bayesian analysis of data from a randomized, double-blind, placebo-controlled, multicenter Phase 3 study (Study 1), which formally integrated treatment success rates from a placebo-controlled Phase 2 study (Study 2). Enrolled adults in both studies were 18 years of age or older and had a confirmed diagnosis of recurrent CDI (one or more episodes in Study 1; two or more episodes in Study 2) which was defined as diarrhea (passage of 3

or more loose bowel movements within a 24-hour period for 2 consecutive days) and a positive stool test for *C. difficile* toxin or toxigenic *C. difficile*, or had at least two episodes of severe CDI resulting in hospitalization within the last year. Enrolled adults were required to have completed at least 10 consecutive days of antibiotic therapy and have their CDI under control (<3 unformed/loose, i.e., Bristol Stool Scale type 6-7, stools/day for 2 consecutive days). A minimum of 24 hours to a maximum of 72 hours (Study 1) or 24 hours to a maximum of 48 hours (Study 2) antibiotic washout period was required prior to administration of the assigned study treatment. In Study 1, enrolled adults were randomized 2:1 to a single dose of Rebyota or placebo respectively. In Study 2, randomization was 1:1:1 to receive two doses of Rebyota, two doses of placebo, or one dose of Rebyota and one dose of placebo, administered 7±2 days apart. Only data from the Rebyota one-dose group and the placebo group were integrated in the Bayesian analysis.

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. In Study 1, a total of 262 adults were randomized and treated, of which 177 adults received Rebyota and 85 received placebo. In this study, 32.8% of adults received Rebyota or placebo for their first recurrence of CDI. In Study 1, 87.4% of adults had received vancomycin alone prior to treatment. In Study 2, 39 adults received one dose of Rebyota and one dose of placebo and 43 adults received two doses of placebo. In this study, 89.0% of adults had received vancomycin prior to treatment.

Treatment success was defined as the absence of CDI diarrhea within 8 weeks of blinded treatment. CDI diarrhea was defined as the passage of ≥ 3 unformed/loose stools in ≤ 24 hours for at least 2 consecutive days and a positive stool test for the presence of *C difficile* toxin at the time of the diarrhea.

In the Bayesian analysis, the estimated rate of treatment success was significantly higher in the Rebyota group (70.6%) than in the placebo group (57.5%) through 8 weeks after completing blinded treatment, resulting in a difference of 13.1 percentage points (95% Credible Interval: 2.3, 24.0) which corresponds to a 99.1% posterior probability that Rebyota is superior to placebo.

References

1. Rebyota [package insert]. Ferring Pharmaceutical Inc. Roseville, Minnesota. Updated November 2022.

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2. Rebyota. Drug Evaluation. Express Scripts. January 2023.

Policy History

Original Effective Date: 10/09/2023
Current Effective Date: 10/09/2023
09/07/2023 Medical Policy Committee review
09/13/2023 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 09/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0780T
HCPCS	G0455, J1440
ICD-10 Diagnosis	A04.71

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.