BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 07/15/24**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE:**
	CURRENT EFFECTIVE DATE: 07/15/24
	LAST CRITERIA REVISION DATE:
NEXT ANNUAL REVIEW DATE: 2ND QTR 2025	**ARCHIVE DATE:**

REBYOTA™ (fecal microbiota, live-jslm)
ZINPLAVA™ (bezlotoxumab)

Non-Discrimination Statement is located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.

This Evidence-Based Criteria provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

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REBYOTA™ (fecal microbiota, live-jslm)
ZINPLAVA™ (bezlotoxumab)

Criteria:

Refer to FDA website for current indications and dosage.

REBYOTA (fecal microbiota, live-jslm)

- **Criteria for initial therapy:** Rebyota (fecal microbiota, live-jslm) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist or Infectious Disease Specialist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of history of recurrences of *Clostridioides difficile* infection (CDI) following standard-of-care antibacterial treatment for recurrent CDI (rCDI) with **ALL** of the following:

   - Diarrhea defined as 3 or more loose stools within a 24 hour period for 2 consecutive days
   - Confirmed with a positive stool test for *C. difficile* toxin or toxigenic *C. difficile*

4. Individual has at least **ONE** of the following other risk factors for recurrent CDI:

   - Greater than 65 years of age
   - Individual is immunocompromised (e.g., active hematologic malignancy, uses an antineoplastic or immunomodulating agent, uses corticosteroids, has received a solid organ transplant, is asplenic, or has an immunodeficiency condition, etc.)
   - Episodes are described as clinically severe CDI (see Definitions section)
   - Infection is due to hypervirulent *Clostridioides difficile* strains (ribotypes 027, 078 or 244)

5. Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for Zinplava

6. Rebyota will be administered 24 to 72 hours after completion of at least 10 days of standard antimicrobial therapy for recurrent CDI treatment

7. Individual will not be using Rebyota for the treatment of CDI

8. Will not be used in combination with other fecal transplants or preventative measures (e.g., Vowst, Zinplava)

Initial approval duration: One single dose (150 mL)

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REBYOTA™ (fecal microbiota, live-jslm)
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- **Criteria for continuation of coverage (renewal request):** Rebyota (fecal microbiota, live-jslm) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist or Infectious Disease Specialist

  2. Continuation of therapy requires meeting **ALL** of the Criteria for initial therapy

  3. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use

  Renewal duration: One single dose (150 mL)

- Rebyota (fecal microbiota, live-jslm) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any **ONE** or more of the following criteria are met:

  1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
  3. Insufficient evidence to support improvement of the net health outcome; or
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
  5. Insufficient evidence to support improvement outside the investigational setting.

  These indications include, *but are not limited to:*

  - Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, or duration.

ZINPLAVA (bezlotoxumab)

- **Criteria for initial therapy:** Zinplava (bezlotoxumab) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist or Infectious Disease Specialist

  2. Individual is 1 year of age or older

  3. Individual has a confirmed diagnosis of *Clostridioides difficile* infection (CDI) currently receiving antibacterial drug treatment and is at high risk for CDI recurrence with **ALL** of the following:

REBYOTA™ (fecal microbiota, live-jslm)
ZINPLAVA™ (bezlotoxumab)

- Diarrhea defined as 3 or more loose stools within a 24 hour period for 2 consecutive days
- CDI confirmed with a positive stool test for *C. difficile* toxin or toxigenic *C. difficile*
- Receiving standard-of-care antibacterial drug (see Definitions section)
- Has at least **ONE** of the following risk factors for recurrent CDI

  a. Greater than 65 years of age
  b. Individual is immunocompromised (e.g., active hematologic malignancy, uses an antineoplastic or immunomodulating agent, uses corticosteroids, has received a solid organ transplant, is asplenic, or has an immunodeficiency condition, etc.)
  c. Episodes are described as clinically severe CDI (see Definitions section)
  d. Infection is due to hypervirulent *Clostridioides difficile* strains (ribotypes 027, 078 or 244)

4. Will not be using use Zinplava for the treatment of CDI

5. Will not be used in combination with other fecal transplants or preventative measures (e.g., Rebyota, Vowst)

Initial approval duration: **One-time infusion at a recommended 10 mg/kg over 60 minutes**
The safety and efficacy of repeat administration of ZINPLAVA in patients with CDI have not been studied

➢ Zinplava (bezlotoxumab) for all other indications not previously listed is considered ***experimental or investigational*** and will not be approved when any **ONE** or more of the following criteria are met:

1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement of the net health outcome; or
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to:*

- Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, or duration.

Description:

Rebyota (fecal microbiota, live-jslm) is indicated for the prevention of *Clostridioides difficile* infection (CDI) recurrence in patients 18 years or older. In addition, the patient completed standard of care antibiotic treatment for the recurrent CDI prior to taking Rebyota; it is not indicated for the treatment of CDI.

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REBYOTA™ (fecal microbiota, live-jslm)
ZINPLAVA™ (bezlotoxumab)

Zinplava (human monoclonal antibody) is indicated to reduce recurrence of CDI in adults and pediatrics patients (1 year of age and older). The patient must be receiving standard-of-care antibiotic treatment, for the recurrent CDI, simultaneously with Zinplava. Zinplava is not indicated for the treatment of CDI.

CDI is caused by the bacterium *Clostridioides difficile*; it is characterized as spore forming, gram-positive, and anaerobic that produces toxins A and B. The infection involves disruption of normal gut flora and the main clinical symptom for diagnosis includes three or more loose stools in 24 hours with no other cause for the acute diarrhea. Patients with the following risk factors have an increased risk of developing CDI; advanced age (65 years and older), hospitalization, weakened immune system, and/or recent antibiotic use. Approximately half a million infections are cause by CDI each year in the United States; one in six of those who get CDI will have a recurrence in the subsequent 2-8 weeks.

A common symptom of CDI is the acute diarrhea as described above. Other signs may include, but not limited to, lower abdominal pain, fever, nausea, and leukocytosis in hospitalized patients. There are a variety of diagnostic laboratory assays that can be used alone or in combination. A few common tests are the nucleic acid amplification (NAAT), immunoassay for *C. difficile* toxins A and B, and cell culture. Demonstration of *C. difficile* toxins or detecting the organism, in addition to the main clinical symptom characterized as acute diarrhea, are the basis to diagnosing CDI.

Definitions:

Standard-of-Care CDI Antibacterial Treatment for Adults

Clinical Presentation	Treatments	Comments
Initial CDI Episode	Fidaxomicin 200 mg by mouth twice daily for 10 days	Preferred Non-severe CDI, Severe CDI
	Vancomycin 125 mg by mouth four times daily for 10 days	Alternative Non-severe CDI, Severe CDI
	Metronidazole 500 mg by mouth three times a day for 10 days	Alternative Non-severe CDI
First CDI recurrence	Fidaxomicin 200 mg by mouth twice daily for 10 days OR Fidaxomicin 200 mg by mouth twice daily for 5 days followed by once every other day for 20 days	Preferred
	Vancomycin 125 mg by mouth by mouth four times daily for 10-14 days, two times daily for 7 days,	Alternative: Tapered/pulsed regimen

	once daily for 7 days, and then once every 2-3 days for 2-8 weeks	
	Vancomycin 125 mg by mouth four times daily for 10 days	Alternative: Standard course IF metronidazole was used for treatment of first episode
	Bezlotoxumab 10 mg/kg intravenously once	Adjunctive: Administer with standard of care treatment Limited date when combined with fidaxomicin Caution in patients with congestive heart failure
Second CDI Recurrence	Fidaxomicin 200 mg by mouth twice daily for 10 days OR Fidaxomicin 200 mg by mouth twice daily for 5 days followed by once every other day for 20 days	
	Vancomycin 125 mg by mouth by mouth four times daily for 10-14 days, two times daily for 7 days, once daily for 7 days, and then once every 2-3 days for 2-8 weeks	Tapered/pulsed regimen
	Vancomycin 125 mg by mouth four times daily for 10 days followed by rifaximin 400 mg three times daily for 20 days	
	Bezlotoxumab 10 mg/kg intravenously once	Adjunctive: Administer with standard of care treatment Limited date when combined with fidaxomicin Caution in patients with congestive heart failure
	Fecal microbiota transplantation	Panel opinion agreed that appropriate antibiotic treatment for at least 2 recurrences should be tried prior to offering fecal microbiota transplantation
Fulminant CDI	Vancomycin 500 mg by mouth or nasogastric tube four times daily for 10 days (if ileus present consider using rectal instillation) PLUS	Fulminant CDI includes patients experiencing hypotension or shock, ileus, megacolon

	Metronidazole 500 mg intravenously every 8 hours (with oral or rectal vancomycin), particularly if ileus is present	

Management of CDI in Adults as Defined by the IDSA and SHEA (2021)

Standard-of-Care CDI Antibacterial Treatment for Children

Clinical Presentation	Treatments	Comments
Initial CDI Episode	Metronidazole 500 mg by mouth three or four times a day for 10 days	7.5 mg/kg/dose three or four times a day Non-severe CDI
	Vancomycin 125 mg four times a day for 10 days	10 mg/kg/dose four times a day Non-severe CDI
	Vancomycin 500 mg by mouth OR rectally for 10 days WITH or WITHOUT Metronidazole 500 mg intravenously three times a day for 10 days	Vancomycin: 10 mg/kg/dose four times a day Metronidazole: 10 mg/kg/dose three times a day Severe or fulminant CDI
First CDI Recurrence	Metronidazole 500 mg by mouth three or four times a day for 10 days	7.5 mg/kg/dose three or four times a day Non-severe CDI
	Vancomycin 125 mg four times a day for 10 days	10 mg/kg/dose four times a day Non-severe CDI
Second CDI Recurrence	Vancomycin 125 mg by mouth by mouth four times daily for 10-14 days, two times daily for 7 days, once daily for 7 days, and then once every 2-3 days for 2-8 weeks	10 mg/kg/dose tapered/pulsed regimen
	Vancomycin 500 mg by mouth four times daily for 10 days FOLLOWED BY Rifaximin 400 mg three times daily for 20 days	Vancomycin: 10 mg/kg/dose four times daily Rifaximin: no pediatric dosing; not approved by the US Food and Drug Administration for use in children <12 years of age

Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the IDSA and SHEA

Severe CDI:

- WBC count greater than 15,000 cells/microliter
- Serum albumin less than 3 g/dL
- Serum creatinine greater than 1.5 times the premorbid level

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History:	**Date:**	**Activity:**
Pharmacy and Therapeutics Committee	05/16/24	Approved Guideline (effective 07/15/24)
Clinical Pharmacist	05/03/24	Development

Coding:

HCPCS: J1440, J0565

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Resources:

Literature reviewed 05/16/24. We do not include marketing materials, poster boards and non-published literature in our review.

1. Alam MU, Mada PK. Clostridioides difficile Infection. In: *StatPearls.* January 2023.; Accessed May 3, 2024. https://www.ncbi.nlm.nih.gov/books/NBK431054/

2. Gerding DN, Johnson S, McDonald LC, 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(7):987-994. doi:10.1093/cid/ciy149

3. Lamont JT, Kelly CP, Bakken JS. Clostridioides difficile infection in adults: Clinical manifestations and diagnosis. In UpToDate, Calderwood SB, Bogorodskaya M (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated November 22, 2022. Accessed April 25, 2024.

4. Lavergne V, Johnson S, 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 Infect Dis*. 2021;73(5):e1029-e1044. doi:10.1093/cid/ciab549

5. Rebyota (fecal microbiota, live-jslm). Prescribing information. Revised by Ferring Pharmaceuticals 11/2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed April 29, 2024.

6. Zinplava (bezlotoxumab). Prescribing information. Revised by Merck Sharp & Dohme LLC 05/2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 1, 2024.

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Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html