VHA Office of Integrated Veteran Care
Clinical Determination and Indication
Fecal Microbiota Products for *Clostridioides difficile* Infections

CDI Number: 00020

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I. Disclaimer

This document is currently in draft and is intended to be used as a reference for non-VA providers and not intended to replace clinical judgment when determining care pathways. These guidelines do not guarantee benefits or constitute medical advice.

II. Clinical Determinations and Indications

a. Indications for Fecal Microbiota Products for *Clostridioides difficile* Infections

Fecal microbiota products (stool derived products) are indicated for the prevention of recurrence of *Clostridioides difficile* infection (CDI), following successful antibiotic treatment for recurrent CDI (rCDI). These products will be considered medically necessary when ALL the following criteria are met:

- *Clostridioides difficile* (*C. difficile*) infection is confirmed by a positive stool test for toxigenic *C. difficile* and presence of greater than or equal to 3 unformed stools within 24 hours for at least 48 hours consecutively
- Veteran has experienced at least two recurrences of CDI within eight weeks of completion of standard antibiotic treatment
    - (i.e., fidaxomicin, vancomycin)
- Veteran has been treated with standard antibiotics for the current episode of CDI with symptom resolution
    - (e.g., clinical symptoms of *C. difficile* such as diarrhea have resolved with standard antibiotic treatment)
- At least one episode of *C. difficile* was treated with fidaxomicin, unless not tolerated or contraindicated
- Received at least one trial of bezlotoxumab with or after standard *C. difficile* treatment, unless not tolerated, contraindicated or not practical due to setting
- VA only approves the use of Food & Drug Administration (FDA) approved stool derived products

Note: This document is in alignment with the VA National Formulary. Please visit the VA Formulary Advisor to access VA Pharmacy Benefits Management Services' resources and additional information on clinical criteria.

- *Criteria for Use:* VOWST and REBYOTA

b. Limitations/Exclusions

VA only allows administration of FDA approved stool-derived products. All other stool-derived products for prevention of recurrent *Clostridioides difficile* infection not listed in section II.a. are considered **not medically necessary**.

Fecal microbiota products are **not indicated** if any of the following are applicable:

- History of severe allergic reactions to any components of REBYOTA or VOWST
  - E.g., glycerol in VOWST; polyethylene glycol in REBYOTA
- History of severe food allergies
- REBYOTA should be avoided in Veterans who are immunocompromised
- VOWST should be avoided in patients with an absolute neutrophil count < 500 cells/mm

REBYOTA and VOWST are not indicated for the treatment of CDI. Use of fecal microbiota products for other conditions are considered investigational, including but not limited to the following:

- Asymptomatic *C. difficile* colonization
- Ulcerative colitis
- Crohn's disease
- Irritable bowel syndrome
- Celiac's disease
- Cirrhosis
- Obesity
- Food allergies

For all conditions/indications not listed in section II.a. of this document, fecal microbiota products such as REBYOTA and VOWST are considered **not medically necessary** due to insufficient evidence of efficacy and safety.

c. Description of Treatment

Stool-Derived Products

The FDA approved the use of two stool-derived products, REBYOTA and VOWST for the prevention of recurrent *C. difficile*. These stool-derived

products should be considered after the patient has experienced at least two recurrences of *C. difficile* infection recurring within eight weeks of completion of standard antibiotic treatment which includes fidaxomicin and/or vancomycin, and at least one trial of bezlotoxumab.

REBYOTA

REBYOTA is a microbiome-based treatment used to prevent recurrent *C. difficile* infections. It is administered 24-72 hours after the last dose of antibiotics. REBYOTA is a single-dose treatment administered rectally. Before administration, patients should be asked to empty their bladder and bowels if possible. The patient should be placed in a left sided position, which is lying on left side with right knee bent and arms resting comfortably. The lubricated administration tube is gently inserted approximately five inches into the rectum, aimed slightly toward the navel. The bag is slowly raised to allow REBYOTA to gradually flow with gravity. Once entire bag has been delivered, the pinch clamp is closed and the tube is slowly withdrawn, keeping the patient in the left sided position for fifteen minutes. Once completed, patients can move freely with no restrictions on using the restroom. The most common adverse reactions reported were abdominal pain, diarrhea, abdominal distention, flatulence, and nausea.

VOWST

VOWST is also a microbiome-based treatment used to prevent recurrent *C. difficile* infections. It is administered 48-96 hours after the last antibiotic dose. Eight hours prior to the first dose of VOWST, patients should be instructed to drink 10 oz of magnesium citrate and not to eat or drink anything within the 8 hours. In clinical studies, 250 mL of polyethylene glycol electrolyte solution was administered instead of the magnesium citrate for participants with impaired renal function. VOWST is administered orally as four capsules taken daily for four consecutive days. Each dose should be taken on an empty stomach, prior to the first meal of the day. The most common adverse reactions reported were abdominal distention, fatigue, constipation, chills, and diarrhea.

III. Background and Supporting Information

The following information is for reference purposes only in accordance with the medical benefits package outlined in 38 C.F.R. § 17.38 (b). Each subsection supports VA's determinations for medical necessity and alignment with generally accepted standards of medical practice.

a. Background Information

Clostridioides difficile (*C. difficile*) Infection

The human intestinal tract contains trillions of bacteria and microorganisms, commonly referred to as the normal "gut microbiota." *Clostridioides difficile* is a bacterium that can be found widely in the environment and transiently in the digestive system of a very small percentage of healthy adults. In some instances (e.g., while or after taking antibiotics to treat infections), the normal microbiota is disrupted and the normal balance of the gut microbiota is altered, and if *C. difficile* is ingested or present in the gut it can multiply and dominate. Elevated amounts of *C. difficile* in the gut leads to the production of toxins, causing diarrhea, abdominal pain, and fevers. Severe cases can result in organ failure and even death.

Certain antibiotics have greater risk for *C. difficile* infection, including clindamycin, cephalosporins, and quinolones (e.g., ciprofloxacin, levofloxacin). Other risk factors for *C. difficile* infection include patients with a weakened immune system or a previous history of *C. difficile* infection, patients staying in a hospital or living in a long-term care facility or nursing home, and patients over the age of 65.

Clostridioides difficile infection is suspected in at-risk patients with new and unexplained unformed or watery and sometimes foul-smelling diarrhea, occurring more than three times per day. The diagnosis for *C. difficile* infection is confirmed through stool testing. *C. difficile* infections are highly contagious for susceptible patients who have had their gut microbiota compromised by antibiotics. Adequate hygiene practices and precautions help minimize bacterial spread, including hand washing, use of personal protective equipment with proper disposal, and use of cleaning agents specific for *C. difficile*.

Approximately 25% of people treated for *C. difficile* infection will have a recurrence of infection. The reason may be that the first infection resolved clinically but the *C. difficile* organism was never completely eradicated or that the subject has acquired a new *C. difficile* infection. The risk of further recurrence increases with each *C. difficile* recurrent episode. After three or more recurrences the risk of another recurrence is greater than 50%.

Management and Treatments

Treatment regimens for *C. difficile* infection are based on their severity. Oral antibiotics such as vancomycin or fidaxomicin are considered appropriate treatment regimens to treat most *C. difficile* infections. Severe complicated cases of *C. difficile* infection also termed fulminant *C. difficile* infection may also require surgical removal of the colon. When patients experience their

second or more recurrence of *C. difficile* infection, stool-derived products, REBYOTA and VOWST, are administered after antibiotics have resolved the symptoms of the infection (e.g., diarrhea).

REBYOTA

REBYOTA was approved by the FDA in November 2022 for the prevention of recurrent *C. difficile*. It is prepared from stool donated by qualified individuals. All donated stool is tested for a panel of transmissible pathogens. Because REBYOTA is made from human stool it may contain food allergens. The potential for REBYOTA to cause an adverse food reaction is unknown at this time.

VOWST

VOWST is the first orally administered fecal microbiota-based product approved by the FDA in 2023 for the prevention of recurrent *C. difficile*. It is prepared from stool donated by qualified individuals and contains live bacterial spores from multiple species. All donated stool is tested for a panel of transmissible pathogens. Because VOWST is made from human stool it may contain food allergens. The potential for VOWST to cause an adverse food reaction is unknown at this time.

b. Research, Clinical Trials, and Evidence Summaries

Randomized controlled trials (RCTs) have shown stool-derived products to be efficacious in preventing rCDI. The following outlines clinical research on available FDA-approved treatment options for the prevention of rCDI.

REBYOTA, a therapy developed by Ferring Pharmaceuticals, was the first FDA-approved, single-dose, microbiota-based live biotherapeutic product for the prevention of rCDI in adults. This approval was based on the study published by Khanna et al. (2022). This randomized, double-blind, placebo-controlled, phase III study evaluated the effects of RBX2660, trade name: REBYOTA, on treatment success or reducing recurrence of *C. difficile* infection. The study included patients from the phase 2 trial PUNCH CD2 in agreement with the FDA due to accrual issues. Patients with a positive stool assay for *C. difficile* and who were previously treated with standard-of-care antibiotics were randomly assigned to receive a subsequent blinded, single-dose enema of RBX2660 (n = 180) or placebo (n = 87). The study found *C. difficile* treatment success rates of 70.4% with RBX2660 versus 58.1% with placebo. Treatment success was defined as the absence of *C. difficile* infection diarrhea within eight weeks of study treatment. This study found that RBX2660 is a safe and effective treatment to treat rCDI following standard-of-care antibiotics, with a sustained response through six months.

Lee et al. (2023) published an integrated safety analysis, providing cumulative safety data from five prospective clinical trials (three phase II trials and two phase III trials) evaluating REBYOTA for preventing rCDI in adults. Among the five trials, 978 study participants received at least one dose of REBYOTA and 83 participants received placebo only. Treatment-emergent adverse events (TEAEs), as defined by an adverse event occurring on or after the day of first treatment, coded using the Medical Dictionary for Regulatory Activities (MedDRA), were reported in 60.2% of placebo participants and 66.4% of REBYOTA participants. Most participants experienced mild or moderate TEAEs, including diarrhea, abdominal pain, and nausea, but were most frequently related to preexisting conditions. Importantly, there were no reported infections for which the causative pathogen was traced to REBYOTA. This integrated safety analysis demonstrates that REBYOTA is a safe and well-tolerated treatment for patients with rCDI.

VOWST, a treatment developed by the biotech company Seres Therapeutics, is an orally administered fecal microbiota product designated for the prevention of rCDI. VOWST received FDA approval based on a phase III development program, including the ECOSPOR III and ECOSPOR IV clinical trials.

ECOSPOR III, published by Feuerstadt et al. (2022), was a multi-center, double-blind, randomized, placebo-controlled trial in which patients who had had three or more episodes of a *C. difficile* infection received either VOWST (n = 89) or placebo (n = 93) for three consecutive days after standard-of-care antibiotic treatment. The study found a statistically significant difference in reduction of CDI recurrence at eight weeks, with 12% of VOWST participants experiencing a *C. difficile* infection recurrence, compared to 40% in the placebo group. Further, at six months post-treatment, 79% of VOWST participants were recurrence-free, compared to 53% in the placebo group. Most adverse events were mild to moderate, with similar numbers between the two groups. The trial concluded that VOWST is superior to placebo in reducing the risk of *C. difficile* infection recurrence.

ECOSPOR IV, authored by Sims et al. (2023), was an open-label, multi-center, single-arm trial conducted to evaluate the safety and rate of CDI recurrence after administration of VOWST through 24 weeks. The trial included 263 participants and found overall low rates of CDI recurrence, consistent with the ECOSPOR III trial rates. Further, no TEAEs led to study withdrawal, as the majority were mild to moderate, including diarrhea, flatulence, and nausea, and resolved without sequelae. This clinical trial reinforced the notion that VOWST is well tolerated in a patient population with recurrent CDI.

c. U.S. Food & Drug Administration (FDA) Information

REBYOTA and VOWST have received Biologics License Application (BLA) approval by the FDA for treatment of adult patients with Clostridioides difficile.

To search for more FDA-approved and licensed biological products, including licensed biosimilar and interchangeable products, regulated by the Center for Drug Evaluation and Research (CDER), please visit the FDA-licensed (approved) Biological Products Database.

Information	Description
BLA Number	55566-9800-0, 55566-9800-1, 55566-9800-2
Drug Name	REBYOTA
Active Ingredients	Donor Human Stool
Company Name	Ferring Pharmaceuticals Inc.
Address	2660 Patton Road Roseville, MN 55113
Approval Date	11/30/2022
Approval Letter	BLA Approval Letter - REBYOTA (fda.gov)

Information	Description
BLA Number	71881-400-12
Drug Name	VOWST
Active Ingredients	DONOR HUMAN STOOL SPORES (ETHANOL TREATED)
Company Name	Seres Therapeutics, Inc
Address	200 Sidney St. Cambridge, MA 02139
Approval Date	04/23/2023
Approval Letter	BLA Approval Letter - VOWST (fda.gov)

d. Medicare Coverage Determinations

There are no available Medicare coverage determinations. VA and Medicare are governed by separate laws and regulations; thus, VA coverage determinations may be different.

IV. Definitions

Term	Definition
Clostridioides difficile (*C. difficile*)	A bacterium commonly found in the normal gut flora of the human intestine that may cause diarrhea and more serious intestinal conditions, such as colitis
Colitis	Inflammation of the colon lining
Colonoscopy	A procedure using a video camera called a colonoscope to view the colon and rectum
Distention	Enlarged or swollen from internal pressure
Ileus (Paralytic ileus)	The inability of the intestine to contract normally and move contents to the intestinal tract
Microbiome	The microorganisms in a particular environment in the body or a part of the body
Sequelae	A condition which is the consequence of a previous disease or injury

V. References

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VI. CDI History/Revision Information

- Explanation of changes to the CDI

Revision Type	Date of Revision	Update(s) Made to CDI
	MM/DD/YYYY	
	MM/DD/YYYY	