

## New Drug Evaluation: oral fecal microbiota spores, live-brpk

**Date of Review:** August 2023

**Generic Name:** fecal microbiota spores, live-brpk

**End Date of Literature Search:** 05/15/2023

**Brand Name (Manufacturer):** Vowst™ (Seres Therapeutics, Inc.)

**Dossier Received:** Not available as of May 2023

### Plain Language Summary:

- Bacteria called *Clostridioides difficile* (also called *C. difficile*) can cause infections in the large intestine. The Food and Drug Administration recently approved a medicine named Vowst™, which can be used to prevent infections caused by *C. difficile* in people who have had these infections more than once. This review looks at evidence for the effectiveness and safety of this new medicine.
- Vowst™ is produced by collecting fecal matter from healthy people. The material is then processed to remove any harmful bacteria, but still allows spores from healthy bacteria to be introduced into the large intestine by the Vowst™ capsule. These spores will then attack toxins from the *C. difficile* bacteria to help prevent another infection.
- In a clinical study of 182 people who had more than one *C. difficile* infection, Vowst™ capsules taken by mouth were better than placebo (sham treatment) at preventing another *C. difficile* infection in the first 8 weeks after treatment.
- The most common adverse events reported with the medicine was stomach pain, gas, constipation, and diarrhea.
- The Oregon Health Plan (OHP) covers Vowst™ if needed. Providers must explain to the OHP why someone needs Vowst™ before it is covered by a process called prior authorization.

### Research Questions:

1. What is the evidence for the efficacy of oral fecal microbiota spores, live-brpk in preventing recurrent *C. difficile* infections (CDI)?
2. What are the harms associated with the use of oral fecal microbiota spores, live-brpk in recurrent CDI?
3. Are there specific subpopulations of patients (specifically by race, antibiotic use, history of CDI, age, socio-economic status, or comorbidities) for which oral fecal microbiota capsules are more effective or associated with more harm than other therapies used to prevent CDI recurrence?

### Conclusions:

- Fecal microbiota spores, live-brpk (VOWST™) oral capsules received FDA approval April 2023.<sup>1</sup> This biologic product was granted Food and Drug Administration (FDA) Priority Review, Breakthrough Therapy, and Orphan Therapy designations.<sup>2</sup> Oral fecal microbiota capsules are indicated to prevent the recurrence of CDI in adults aged 18 years and older following completion of standard-of-care (SOC) antibacterial treatment for recurrent CDI.<sup>1</sup>
- The safety and efficacy of oral fecal microbiota, live-brpk product was evaluated in the ECOSPOR III randomized controlled trial (RCT).<sup>3</sup> This was a phase 3, double-blind, multi-center, placebo-controlled study conducted at 56 sites in the United States and Canada.<sup>3</sup> In this trial, 182 people with 3 or more

recurrent CDIs within 12 months were randomized to receive either 4 capsules of oral fecal microbiota or matched placebo once daily for 3 days following CDI antibiotic treatment (oral vancomycin or fidaxomicin).<sup>3</sup>

- The primary efficacy endpoint of the RCT was CDI recurrence up to 8 weeks after initiation of treatment.<sup>3</sup> Low-quality evidence showed CDI recurrence was lower in patients who received oral fecal microbiota compared to placebo-treated patients (12% vs. 40%; difference: 28%; relative risk [RR], 0.32; 95% confidence interval [CI] 0.18 to 0.58;  $p < 0.001$ ; number needed to treat [NNT] = 4).<sup>3</sup> Similar results were observed regardless of age or initial antibiotic used to treat CDI.<sup>3</sup>
- Adverse events related to, or possibly related to, oral fecal microbiota or placebo occurred in slightly more than half of the patients in each group in the RCT (51% vs. 52%, respectively).<sup>3</sup> The most common adverse events were gastrointestinal (GI) disorders (i.e., flatulence, abdominal pain, abdominal distension, constipation, and diarrhea), most of which were mild to moderate in nature.<sup>3</sup>
- Most of the patients enrolled in the RCT were White. The safety and efficacy of oral fecal microbiota capsules has not been sufficiently studied in Black, Asian, or Pacific Islander populations, or in pediatric patients. Age greater than 65 years did not appear to be a factor in safety or efficacy. Other factors are unknown.

#### **Recommendations:**

- Maintain oral fecal microbiota capsules as non-preferred on the Practitioner-Managed Prescription Drug Plan (PMPDP) subject to prior authorization (PA).
- Add oral fecal microbiota capsules to the “Prevention of *C. difficile* Recurrence” clinical PA criteria. Update criteria to incorporate step therapy with a fecal microbiota transplant before use of bezlotoxumab.
- No PDL changes recommended after evaluation of costs in executive session.

#### **Background:**

Medications FDA-approved to treat and prevent CDI were reviewed by the Pharmacy and Therapeutics (P & T) Committee at the June 2023 meeting. Evidence for the efficacy and safety of the recently FDA-approved fecal microbiota enema (REBYOTA) was presented. After reviewing the evidence, the committee made the following recommendations:

- Maintain fidaxomicin as a non-preferred drug on the PMPDP with PA criteria to ensure appropriate utilization.
- Maintain fecal microbiota enema as a non-preferred drug on the PMPDP subject to PA. Create a new set of PA criteria titled “Prevention of *C. difficile* Recurrence” and include bezlotoxumab infusion and fecal microbiota enema in the new PA.

*C. difficile* infection is one of the most common healthcare-associated infections in the United States and is associated with 15,000 to 30,000 deaths annually due to consequences of severe diarrhea and colitis.<sup>2,4</sup> The pathogenesis of CDI typically occurs as a two-step process: (1) the disruption of the microbiome, a diverse ecosystem that provides essential functions for the host; and (2) exposure to *C. difficile* spores.<sup>5</sup> The primary risk factor for disease development is antibiotic use, which contributes to the pathophysiology of CDI by creating ecologic gaps within the microbiome.<sup>5</sup> The loss of microbial diversity reduces colonization resistance and negatively impacts microbe-associated functions that are key to host defense.<sup>5</sup> When the balance of microorganisms in the gut is changed, *C. difficile* is allowed to multiply and release toxins causing diarrhea, abdominal pain and fever, and in some cases, organ failure and death.<sup>2</sup> In a disrupted microbiome, there is an increase in the abundance of proinflammatory Gram-negative *Proteobacteria* and a decline in the abundance of beneficial spore-forming *Firmicutes* species that play a dominant role in gut health.<sup>5</sup> The loss of Gram-positive *Firmicutes* leads to microbe-associated changes that support favorable conditions for the spore germination and bacterial growth of *C. difficile*.<sup>5</sup>

After recovering from initial CDI, individuals may get recurrent CDI.<sup>2</sup> Risk factors for recurrent CDI include age 65 years and older, recent antibiotic use, renal insufficiency, history of previous CDIs, prolonged hospital stays, proton pump inhibitor use, and lack of sufficient immune response to *C.difficile* toxins.<sup>4</sup> Recurrent CDI is defined by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) as an episode of CDI that occurs less than 8 weeks after the onset of a previous CDI episode, if CDI symptoms from the previous episode were resolved.<sup>6</sup> Approximately 20% of patients will experience an initial recurrence, and rates of further recurrences continue to increase significantly to greater than 40% after each episode.<sup>5,7</sup> For the first recurrence of CDI, 10-day oral vancomycin regimen or a 10-day course of fidaxomicin is recommended if vancomycin was used for the initial episode.<sup>6</sup> For non-severe CDI in children, either weight-based metronidazole or oral vancomycin dosing is recommended for an initial episode or first CDI recurrence.<sup>8</sup> For severe CDI in children, oral vancomycin is recommended over metronidazole by IDSA/SHEA (2017).<sup>8</sup>

Bezlotoxumab, an anti-toxin B monoclonal antibody, received FDA-approval in 2016 for prevention of CDI recurrence in combination with CDI SOC antibiotics (oral vancomycin or fidaxomicin). Bezlotoxumab is not indicated for the treatment of CDI. It is only approved for use in combination with antibiotics in adults at high risk for CDI recurrence as a single 10 mg/kg intravenous (IV) infusion.<sup>9</sup> The evidence for the safety and efficacy of bezlotoxumab was reviewed by the P & T Committee at the May 2018 meeting. Considering the high cost of bezlotoxumab and the minimal benefits over placebo in patients at low risk of recurrent CDI, the American College of Gastroenterology (ACG) 2021 guidance recommends bezlotoxumab be considered for patients in whom the observed benefits in clinical trials were greatest, including those aged 65 years or older with at least one of the following additional risk factors: experiencing a second episode of CDI within the past 6 months, immunocompromised, or severe CDI (conditional recommendation, moderate-quality evidence).<sup>7</sup> The IDSA/SHEA 2021 guidance is similar to ACG guidance and recommends bezlotoxumab as a co-intervention along with SOC antibiotics rather than SOC antibiotics alone for patients with a recurrent CDI episode within the last 6 months (conditional recommendation, very low certainty of evidence).<sup>6</sup> Data on the use of bezlotoxumab when fidaxomicin is used as the SOC antibiotic are limited as most patients in clinical trials of bezlotoxumab received vancomycin.<sup>6</sup>

If there are 2 or more CDI recurrences despite appropriate antibiotic treatments, fecal microbiota transplant (FMT) is recommended by IDSA/SHEA (2017).<sup>8</sup> Transplantation occurs by instillation of processed stool donated by a healthy volunteer via nasogastric/nasoduodenal tube, colonoscopy, enema, or capsule.<sup>10</sup> An important barrier to the integration of FMT into regular clinical practice is the heterogeneity of administration routes and lack of standardization of FMT guidance.<sup>10</sup> Standardization of the methodological components of FMT includes: donor screening, stool preparation, storage, and instillation route.<sup>10</sup> The efficacy of FMT after SOC antibiotics for preventing recurrent CDI has been described in numerous case series and RCTs.<sup>7</sup> There have been a few trials comparing the effectiveness of different FMT delivery modalities.<sup>7</sup> The choice of the most appropriate route of instillation should be driven partly by the options available to the provider, the preferences of the patient, and the clinical circumstances.<sup>7</sup> It's not clear how current FMT processes will change with 2 FDA-approved products commercially available.

A 2018 joint guideline developed by the British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) provided recommendations for best practices for the provision of FMT in adults with CDI before commercial products were available.<sup>11</sup> Strength of recommendations and quality of evidence for which patients are the best candidates for FMT are as follows:

- FMT should not be administered as initial treatment for CDI (strong recommendation, low-quality evidence).<sup>11</sup>
- FMT should be offered to patients with recurrent CDI who have had at least 2 recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe CDI (strong recommendation, high-quality evidence).<sup>11</sup>
- FMT should be considered in cases of severe CDI (strong recommendation, moderate-quality evidence).<sup>11</sup>

The ACG 2021 guidance includes a recommendation that patients experiencing their second or more recurrence of CDI be treated with FMT to prevent additional recurrences (strong recommendation, moderate-quality evidence).<sup>7</sup> This recommendation is supported by the United Kingdom’s National Institute for Health and Care Excellence (NICE) 2022 guidance.<sup>12</sup>

In June 2019, the FDA released a statement warning of the risks associated with FMT due to transmission of multi-drug resistant organisms.<sup>13</sup> Two immunocompromised adults who received investigational FMT developed invasive infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E. Coli*); of the 2 adults, one of the individuals died.<sup>13</sup> Another warning was issued March 2020, reporting 6 additional cases of transmission of antibiotic-resistant organisms (enteropathogenic *E. coli* in 2 cases and Shigatoxin-producing *E. coli* in 4 cases) via FMT.<sup>14</sup> In April 2020, the FDA issued a safety alert requiring testing of stool donors for SARS-CoV-2 virus due to possible risk of viral transmission from donor to recipient.<sup>15</sup> In August 2022, a similar safety alert regarding possible transmission of monkeypox virus via FMT was published to recommend additional donor screening parameters.<sup>16</sup>

See **Appendix 1 for Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

#### **Clinical Efficacy:**

Fecal microbiota spores, live-brpk (VOWST) oral capsules received FDA approval April 2023. This is the second fecal microbiota product approved by the FDA and the first that is administered orally. Oral fecal microbiota capsules are indicated to prevent the recurrence of CDI in adults aged 18 years and older following completion of SOC antibacterial treatment for recurrent CDI.<sup>1</sup> Oral fecal microbiota capsules are not indicated for treatment of CDI.<sup>1</sup> The product is composed of live purified *Firmicutes* bacterial spores in a suspension manufactured from human fecal matter sourced from qualified donors.<sup>1,3</sup> Live purified *Firmicutes* bacterial spores are theorized to limit *C. difficile* spore germination.<sup>3</sup> Sustained clinical responses are associated with the engraftment of *Firmicutes* bacteria.<sup>5</sup> Donors are screened via a questionnaire, physical examination, and blood and stool testing for pathogens of concern.<sup>4</sup> Stool donations are processed with an ethanol solution to kill fecal organisms that are not spores.<sup>4</sup> Unlike most vegetative organisms, spores are resistant to gastric acid, heat, and a range of chemical and physical changes, exhibiting exceptional stability during manufacturing and drug product storage.<sup>5</sup>

The recommended dose of oral fecal microbiota is 4 capsules taken by mouth once daily on an empty stomach prior to the first meal of the day for 3 consecutive days.<sup>1</sup> Prior to taking the first dose, the GI tract should be cleared of residual antibiotic with the administration of 296 mL of magnesium citrate the day before and 8 hours prior to taking the first dose of fecal microbiota capsules.<sup>1,3</sup> In clinical studies, people with impaired renal function received 250 mL of polyethylene electrolyte solution.<sup>1</sup> The manufacturer also recommends patients not eat or drink, except for a small amount of water, for at least 8 hours before taking the first dose.<sup>1</sup> The mechanism of action of fecal microbiota has not been established; although it is hypothesized that replacement of healthy gut microbiome will help prevent recurrent CDIs.<sup>5</sup>

ECOSPOR III was a Phase 3, double-blind, placebo-controlled, RCT of 182 adults with 3 or more CDI episodes who were randomized to receive either oral fecal microbiota or placebo (4 oral capsules daily for three days) following completion of SOC antibiotic treatment (oral vancomycin or fidaxomicin). The RCT was conducted at 56 sites in the United States and Canada.<sup>3</sup> The recurrence of CDI was defined by investigators as diarrhea (3 or more unformed stools per day) for at least 2 consecutive days, a positive stool *C. difficile* toxin test, and resolution of symptoms after receiving 10 to 21 days of SOC antibiotic therapy.<sup>3</sup>

Before donating stool, 4 donors underwent an extensive health examination, including personal and family medical history, laboratory chemical and hematologic screening, urinalysis, and viral, bacterial, and parasite testing of blood and stool to generate 4 lots of fecal microbiota.<sup>3</sup> Donated stool was obtained before the

onset of the COVID-19 pandemic.<sup>3</sup> Because vancomycin and fidaxomicin can persist in the gastrointestinal tract for up to 5 to 7 days after discontinuation, 296 mL of magnesium citrate was administered the night before fecal microbiota treatment to limit inactivation of species of bacteria present in the fecal microbiota regimen.<sup>3</sup> Patients who could not take magnesium citrate due to renal impairment were given 250 mL of polyethylene glycol electrolyte solution.<sup>3</sup> Patients were contacted weekly via telephone by investigators to assess onset of adverse events or diarrhea. Patients were asked to complete a daily diarrhea log when they experienced 1 or more daily episodes of diarrhea. If more than 3 unformed stools per day over 2 consecutive days recurred, patients were instructed to return to the clinic for stool testing at a central laboratory and clinical evaluation. Investigators determined recurrence of CDI after completing a patient assessment. Of the 182 enrolled patients, 149 (82%) completed 8 weeks of follow-up.<sup>3</sup> Five of the 89 patients (6%) in the oral fecal microbiota group and 28 of 93 (30%) in the placebo group withdrew before week 8.<sup>3</sup> The most common reason for withdrawal from the trial was CDI recurrence, which was more common in the placebo group than in the oral fecal microbiota group (24% and 3%, respectively).<sup>3</sup>

The primary efficacy outcome was CDI recurrence up to 8 weeks after initiation of treatment.<sup>3</sup> CDI recurrence was defined as onset of more than 3 watery stools per day over 2 days, positive stool *C. difficile* toxin assay, and persistence of diarrhea until initiation of antibiotic treatment.<sup>3</sup> Patients who were lost to follow-up, discontinued participation in the trial prematurely, or died without a recurrence of *C. difficile* infection before 8 weeks after treatment were defined as having a *C. difficile* infection recurrence.<sup>3</sup> Low-quality evidence showed CDI recurrence was lower in patients who received oral fecal microbiota compared to placebo-treated patients (12% vs. 40%; difference: 28%; RR, 0.32; 95% CI 0.18 to 0.58; p<0.001; NNT=4).<sup>3</sup> Administration of fecal microbiota led to less frequent CDI recurrence than placebo in analyses stratified according to age (age <65 years: RR, 0.24; 95% CI, 0.07 to 0.78 and age ≥65 years: RR, 0.36; 95% CI, 0.18 to 0.72) and antibiotic received (oral vancomycin: RR, 0.41; 95% CI, 0.22 to 0.79 and fidaxomicin: RR, 0.09; 95% CI, 0.01 to 0.63).<sup>3</sup> Most recurrence events occurred rapidly, with onset as early as day 4 after randomization.<sup>3</sup> Of the 48 recurrences that occurred in the overall trial population by week 8, a total of 36 (75%) occurred within 2 weeks and 41 (85%) occurred within 4 weeks after administration of oral fecal microbiota or placebo.<sup>3</sup> In The secondary analysis of percent of patients with recurrent CDI at 24 weeks, the rate of recurrence in the active comparator arm had almost doubled to 21% vs. 47% in the placebo-treated arm (RR, 0.46; 95% CI 0.30 to 0.73; p<0.001).<sup>3</sup>

Limitations of this trial include the very low representation of non-White patients. Considering the extent of CDI in the United States and Canada, the population recruited for this study was small. Stool specimens were not obtained before antibiotic treatment, so the full effect of fecal microbiota on the pre-antibiotic microbiome is unknown.<sup>3</sup> Efficacy and safety of oral fecal microbiota have not been established in pediatric patients.

Details for the RCT which contributed to the safety and efficacy data of oral fecal microbiota capsules to prevent recurrent CDI are described in **Table 3**.

#### **Clinical Safety:**

Adverse events that were related to, or possibly related to, fecal microbiota or placebo occurred in slightly more than half of the patients in each group in the RCT (51% vs. 52%).<sup>3</sup> The most common adverse events were GI disorders (i.e., flatulence, abdominal pain, abdominal distension, constipation, diarrhea), most of which were mild to moderate in nature.<sup>3</sup> Three deaths occurred in the fecal microbiota group, none of which were deemed by the blinded investigators to be drug-related.<sup>3</sup> Adverse effects reported in the RCT are summarized in **Table 1**.

**Table 1.** Adverse reactions reported in 5% or more of patients treated with fecal microbiota oral capsules compared with placebo<sup>1</sup>

Adverse Reaction	Fecal Microbiota Oral Capsules (n=90)	Placebo (n=92)
<i>Solicited: recorded by participants in a diary for 7 days after completing a 3-day regimen of study drug or placebo</i>		
Abdominal Distension	31.1%	29.3%
Fatigue	22.2%	21.7%
Constipation	14.4%	10.9%
Chills	11.1%	7.6%
<i>Unsolicited: recorded by investigator queries during visits over 8 weeks after first dose of study drug</i>		
Diarrhea	10.0%	4.3%

Look-alike / Sound-alike Error Risk Potential: No results available

**Comparative Endpoints:**

Clinically Meaningful Endpoints:

- 1) Resolution of CDI-associated diarrhea without CDI recurrence within 8 weeks
- 2) Sustained treatment response (no CDI 6 months after last dose)
- 3) Serious adverse events
- 4) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Treatment success (absence of CDI diarrhea within 8 weeks of treatment)

**Table 2. Pharmacology and Pharmacokinetic Properties.**

Parameter	
Mechanism of Action	Not established: theoretical supposition that biotherapeutic product repopulates and restores diversity of gut microbiome to suppress <i>C. difficile</i> overgrowth
Oral Bioavailability, Distribution, and Protein Binding	Not Applicable
Elimination, Half-Life and Metabolism	

**Table 3. Comparative Evidence Table.**

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Feuerstadt P, et al. <sup>3</sup>  ECOSPOR III  Phase 3, DB, MC, PC, RCT	1. Fecal microbiota: 4 capsules PO once daily x 3 days  2. Placebo: 4 capsules PO once daily x 3 days  *All patients received 296 mL of magnesium citrate (or 250 mL of polyethylene glycol for patients with renal impairment) the night before treatment.	<u>Demographics:</u> -Mean age: 65.5 yo -Race: White: 93% Black: 4% Asian: 1% Other: 3% -Female: 60% -Outpatient: 99% -3 rCDI episodes: 60% -Greater than 4 rCDI episodes: 40% -Previous antibiotic regimen: Vancomycin: 73% Fidaxomicin: 27%  <u>Key Inclusion Criteria:</u> - Adults ≥18 yo with ≥ 3 episodes of rCDI within previous 12 mos - Positive <i>C. difficile</i> stool toxin assay - Completion of 10 to 21 days of PO vancomycin or fidaxomicin with resolution of diarrhea  <u>Key Exclusion Criteria:</u> -Toxic megacolon and/or small bowel ileus, history of IBS or active inflammatory bowel disease - Currently receiving ≥ 20 mg of prednisone or equivalent for > 2 weeks - Prior receipt of FMT	<u>ITT:</u> 1. 89 2. 93  <u>Attrition:</u> 1. 5 (6%) 2. 28 (30%)	<u>Primary Endpoint:</u> Percent of patients with rCDI at 8 weeks 1. 11 (12%) 2. 37 (40%) Difference: 28% RR 0.32; 95% CI 0.18 to 0.58; P<0.001  <u>Secondary Endpoints:</u> Percent of patients with rCDI at 12 weeks 1. 16 (18%) 2. 43 (46%) RR 0.40; 95% CI 0.24 to 0.65; P<0.001  Percent of patients with rCDI at 24 weeks 1. 19 (21%) 2. 44 (47%) RR 0.46; 95% CI 0.30 to 0.73; P<0.001	28%/4  28%/4  26%/4	<u>Any AE</u> 1. 84 (93%) 2. 84 (91%)  <u>TEAE</u> 1. 46 (51%) 2. 48 (52%)  <u>Serious AE</u> 1. 7 (8%) 2. 15 (16%)  <u>GI-related AE</u> 1. 79 (88%) 2. 80 (87%)  95% CI NR for all	NA  NA  NA	<b>Risk of Bias (low/high/unclear):</b> <u>Selection Bias:</u> Low. Randomized 1:1 via IRS to active drug or placebo. Stratified by antibiotic regimen and age (< 65 yo or ≥ 65 yo). Baseline characteristics balanced between groups except for gender (53% females enrolled in placebo arm vs. 67% enrolled in active comparator arm). <u>Performance Bias:</u> Low. Participants and investigators blinded to treatment assignment. <u>Detection Bias:</u> Low. Placebo capsules matched fecal microbiota capsules in appearance. Blinded investigators determined if patients experienced rCDI. <u>Attrition Bias:</u> High. Attrition rates were higher in the placebo group, due to higher rates of rCDI in this group. Data missing for patients who withdrew early was imputed as rCDI. <u>Reporting Bias:</u> Low. Protocol available online. All outcomes reported as described. <u>Other Bias:</u> Unclear. Research supported by manufacturer. Many of the investigators report financial support or grants from the manufacturer.  <b>Applicability:</b> <u>Patient:</u> Enrolled adults were primarily White. No data for pediatric patients. <u>Intervention:</u> FDA-approved regimen used. <u>Comparator:</u> Placebo was used to establish efficacy. Comparison to non-FDA approved fecal microbiota formulations or fecal microbiota enema for prevention of rCDI is unknown. <u>Outcomes:</u> Treatment success (defined as symptom resolution) at 8 weeks is a clinically relevant endpoint as defined in guidelines for rCDI. <u>Setting:</u> 56 sites in the US and Canada
<u>Abbreviations:</u> AE = adverse event; ARR = absolute risk reduction; CDI = <i>C. difficile</i> infection; CI = confidence interval; DB = double blind; FDA = Food and Drug Administration; FMT = fecal microbiota transplant; GI = gastrointestinal; HR = hazard ratio; IBS = irritable bowel syndrome; IRS = interactive response system; ITT = intention to treat; mos = months; MC = multi-center; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = placebo-controlled; PO = oral; PP = per protocol; rCDI = recurrent <i>C.difficile</i> infection; RCT = randomized controlled trial; RR = relative risk; TEAEs = treatment-emergent adverse events; yo = years old.								

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## Appendix 1: Prescribing Information Highlights

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VOWST™ safely and effectively. See full prescribing information for VOWST.

**VOWST (fecal microbiota spores, live-brpk) capsules, for oral administration**

Initial U.S. Approval: YYYY

### INDICATIONS AND USAGE

VOWST is indicated to prevent the recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older following antibacterial treatment for recurrent CDI (rCDI). (1)

Limitation of Use:

VOWST is not indicated for treatment of CDI.

### DOSAGE AND ADMINISTRATION

#### For oral administration only. (2)

- Prior to taking the first dose:
  - Complete antibacterial treatment for rCDI 2 to 4 days before initiating treatment with VOWST. (2.1)
  - Drink 296 mL (10 oz) of magnesium citrate on the day before and at least 8 hours prior to taking the first dose of VOWST. In clinical studies, participants with impaired kidney function received polyethylene glycol electrolyte solution (250 mL GoLYTELY, not approved for this use). (2.1)
- The dosage of VOWST is 4 capsules taken orally once daily for 3 consecutive days. (2.2)
- Take each dose (4 capsules) on an empty stomach prior to the first meal of the day. (2.2)

### DOSAGE FORMS AND STRENGTHS

Capsule. A single dose is 4 capsules. (3)

### CONTRAINDICATIONS

None. (4)

### ADVERSE REACTIONS

Most common adverse reactions (reported in ≥5% of participants) were abdominal distension (31.1%), fatigue (22.2%), constipation (14.4%), chills (11.1%) and diarrhea (10.0%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aimmune Therapeutics, Inc. at 1-833-246-2566 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

Antibacterials should not be administered concurrently with VOWST. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: M/YYYY

Appendix 2: Prior Authorization Criteria

Prevention of Recurrent *Clostridioides difficile*-Associated Infection

**Goal(s):**

- To optimize appropriate prevention of recurrent *Clostridioides difficile*-associated infection (CDI). Recurrent CDI is defined by Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) as an episode of CDI that occurs less than 8 weeks after the onset of a previous CDI episode, if CDI symptoms from the previous episode were resolved.

**Length of Authorization:**

- Bezlotoxumab (ZINPLAVA): One-time infusion
- Fecal microbiota, live-jslm (REBYOTA): One-time rectal administration
- Oral fecal microbiota spores, live-brpk (VOWST): 4 capsules once daily x 3 days (12 capsules total)

**Requires PA:**

- Drugs approved to prevent recurrence of CDI:
  - Bezlotoxumab for intravenous infusion (physician administered and pharmacy claims)
  - Fecal microbiota, live-jslm suspension for rectal administration (physician administered and pharmacy claims)
  - Oral fecal microbiota spores, live-brpk (pharmacy claims)

**Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the indication match the FDA-approved indication?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3. Is the request for an FDA approved-age?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; medical appropriateness

## Approval Criteria

4. Is the request for bezlotoxumab?	<b>Yes:</b> Go to #5	<b>No:</b> Go to #8
5. Is this recurrent of <i>Clostridioides difficile</i> -associated infection (CDI) within 6 months of CDI <b>OR</b> Is the patients presenting with a primary CDI episode and has other risk factors for CDI recurrence (such as age ≥65 years, immunocompromised host, or severe CDI on presentation)? *  *Per 2021 IDSA/SHEA guidance <sup>1</sup>	<b>Yes:</b> Go to #6	<b>No:</b> Pass to RPh. Deny; medical appropriateness
6. Has the patient received either the fecal microbiota rectal suspension or a 3 day-course of the oral fecal microbiota spores?	<b>Yes:</b> Go to #7	<b>No:</b> Pass to RPh. Deny; medical appropriateness
7. Is the patient currently receiving vancomycin or fidaxomicin?	<b>Yes:</b> Approve one dose	<b>No:</b> Pass to RPh. Deny; medical appropriateness
8. Is this the second or more recurrence of a <i>Clostridioides difficile</i> -associated infection? *  *Per 2021 ACG and 2022 NICE guidance <sup>2,3</sup>	<b>Yes:</b> Go to #9	<b>No:</b> Pass to RPh. Deny; medical appropriateness
9. Will the patient have recently completed a 10-day course of vancomycin or fidaxomicin prior to starting therapy?	<b>Yes:</b> Approve for 1 course of treatment (see Length of Authorization)	<b>No:</b> Pass to RPh. Deny; medical appropriateness

1. Johnson S, Lavergne V, 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):1029-e1044.
2. Kelly CR, Fischer M, Allegretti JR, et al. American College of Gastroenterology Clinical Guidelines: Prevention, Diagnosis, and Treatment of *Clostridioides difficile* Infections. The American Journal of Gastroenterology. 2021; 116(6):1124-1147.

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3. National Institute for Health and Care Excellence (NICE): Fecal microbiota transplant for recurrent *Clostridioides difficile* infection. August 31, 2022.  
<https://www.nice.org.uk/guidance/mtg71> Accessed February 27, 2023.
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*P&T / DUR Review:* 8/23 (DM); 6/23  
*Implementation:* 9/1/23; 7/1/23