Fecal microbiota spores, live-brpk (VOWST)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- VOWST (SER-109), or fecal microbiota spores, live-brpk, is a bacterial spore suspension in capsules for oral administration. VOWST is manufactured from human fecal matter sourced from qualified donors and is routinely screened for a panel of transmissible pathogens. The spore suspension is generated by treating fecal matter with ethanol to kill live organisms that are not spores, then filtration to remove residual solids and ethanol. Each capsule contains a standard amount of Firmicutes spore forming colony units.
- VOWST was approved by FDA on April 26th, 2023, for the prevention of recurrence of *Clostridioides difficile* infection (CDI) after completion of antibiotic treatment for recurrent CDI in individuals 18 years of age and older.

Dosage Form(s) Under Review

- Capsules, provided in a bottle of 12 capsules
- The dose is 4 capsules taken orally once daily for 3 consecutive days, on an empty stomach prior to the first meal of the day
- VOWST is started 2-4 days after completion of CDI treatment. **296 mL of magnesium citrate should be taken the day before the first dose of VOWST. For those unable to take Mg Citrate, 250 mL of polyethylene glycol should be used.**

Clinical Evidence Summary

Efficacy Considerations

- Effectiveness of VOWST was based on two Phase 3 trials, one randomized, double-blind, placebo controlled (DB, PC RCT) and one randomized, open-label trial. Included were adults with recurrent CDI (rCDI), with a total of 3 or more episodes of CDI within 12 months. Enrollment challenges precluded the proposed enrollment of 320 subjects with revised sample size of 182.
    - **Blinded Phase 3 trial**: 3 daily doses of VOWST (4 capsules) versus placebo in patients with at least 3 CDI episodes within 12 months. The primary efficacy endpoint was rCDI within 8 weeks of completion of treatment.
    - **Open-label Phase 3 trial:** phase 3 RCT of a **single dose of VOWST versus placebo** in patients with **ONE** or more recurrences after primary episode
- Additional efficacy data are summarized in Table 1.

Table 1: VOWST Efficacy Results From Clinical Trials

Reference	Study Design/Intervention	Endpoints	Patient Demographics	Results
Feuerstadt, 2022 (ECOSPOR III) (SERES-012)	Randomized, controlled Phase 3 Trial Adults with 3 or more CDI episodes within 12 months and symptoms resolved on 10-21 days of CDI antibiotics (VAN or FDX) **Select Exclusions:** toxic megacolon, history active IBD w/in 3 months/ absolute neutrophil count < 500 cells/ml^3, need for concomitant antibiotics Patients randomized 1:1 VOWST or placebo, 4 capsules daily x 3 days ***10 ounces Mg citrate given the night before treatment (or polyethylene glycol for pts who couldn't take MgCit)***	**Primary Outcome: Treatment success,** defined as absence of rCDI within 8 weeks after last dose. Patients who died or were lost to follow-up were defined as rCDI Primary analysis in ITT population (all randomized patients) **VOWST**: n=89 **Placebo:** n=93	**Demographics:** **Median age** 66 yrs. Female: VOWST: 67% Placebo: 53% **Number of episodes:** **3 episodes** VOWST: 55% Placebo: 66% **4 or more episodes** VOWST: 44% Placebo: 34% **Primary CDI treatment** **Vancomycin** VOWST: 72% Placebo: 74% **Fidaxomicin** VOWST: 28% Placebo: 26%	**Efficacy Results:** **Recurrence within 8 weeks** VOWST: 12% Placebo: 40% *RR 0.32 (95% CI 0.18-0.58*) **Subgroups:** **Patients 65 years or older:** VOWST: 17% Placebo: 46% *RR 0.36 (95% CI 0.18-0.72)* **Vancomycin as CDI Rx** VOWST: 16% Placebo: 38% **Fidaxomicin as CDI Rx** VOWST: 4% Placebo: 46% **Sustained clinical response (8 wks)** VOWST: 88% Placebo: 60% **By 24 wks. 21% of VOWST and 47% of placebo recipients had rCDI-** ***most occurred within 12 weeks***
Sims 2022 (ECOSPOR IV) (SERES-013)	Phase 3, open-label extension of ECOSPOR III (those who recurred within 8 weeks: cohort 1) as well as de novo patients with rCDI (cohort 2). Patients in cohort 2 had to have at least 1 rCDI episode Cohort 1: 4 patients who received VOWST and 25 placebo. Cohort 2 (n=234) **Intervention:** 4 capsules of VOWST for 3 days	**Primary endpoint:** rCDI within 8 weeks of treatment All subjects (n=263) *SERES-013 was primarily designed to increase the safety database for VOWST. Given lack of placebo comparator, efficacy was descriptive only*	**Demographics** (combined cohort 1 and 20 Female: 68% Median age: 64 yrs. **Vancomycin therapy for CDI episode: 73%** Fidaxomicin: 27%	**Recurrence within 8 weeks** **All subjects:** 9% **Cohort 1:** 14% **Cohort 2:** 8% *All patients had previously responded to CDI therapy (10-42 days of VAN or 10-25 days of FDX), but details about exact treatment or number of previous rCDI episodes not available*

SERES-004 (ECOSPOR)	Phase 2, DB, PC, RCT
	
	Patients with 3 or more episodes within 9 months who had responded to CDI therapy
	
	Randomized 2:1 VOWST or placebo – single dose of 4 capsules
		Primary endpoint: rCDI by 8 weeks (either PCR or toxin test)
		
		VOWST (n=59)
		Placebo (n=30)
			Age < 65: 48%
			
			67% female
			
			53% had 3 episodes CDI
			
			29% had 4 episodes CDI
			
			Vancomycin therapy for CDI episode: 79%
			
			81% diagnosed by PCR
				Recurrence:
				VOWST: 44%
				Placebo: 53%
				- **No difference in those < 65 yrs**
				- **Subgroup ≥ 65 years:**
				  - **VOWST:** 45%
				  - **Placebo:** 80%

Efficacy summary:

- VOWST was approved by the FDA as prevention for rCDI largely based on results of a single Phase 3 trial, with supportive data from a phase 2 blinded RCT and Phase 3 open-label extension studies.
- Available evidence, while limited, suggests that VOWST provided additional protection against rCDI after successful treatment. While most patients received VAN as their primary therapy, a significant reduction was also shown in those who received FDX as their primary therapy, although the number of patients was small.
- In the subgroup aged 65 years and older, VOWST also showed a significant reduction in rCDI
- Given exclusion of patients with recent active IBD / IBS or severe neutropenia, efficacy in these populations cannot be determined

Safety Considerations

- Safety data comes from the ECOSPOR trials, from 349 adults who received three daily doses of VOWST and 111 who received a 1-day regimen. The majority of those patients (n=259) comes from the open-label SERES-013, and therefore lack a comparator.
- **Contraindications:** None
- **Other warnings / precautions**:
    - **Transmissible infectious agents**: VOWST carries risk for transmitting infectious agents as it is manufactured from human fecal matter
        - Of note, patients an absolute neutrophil count < 500 cells/uL were excluded from most trials as were patients with toxic megacolon or small bowel ileus. 29% of patients in ECOSPOR III were immunocompromised.
        - FDA released several recent safety alerts related to transmission of infection due to shiga-toxin producing *E.coli*, extended-spectrum beta-lactamase producing *E.coli*, norovirus and potential transmission for SARS-CoV-2 and monkeypox, highlighting the need for rigorous screening and appropriate patient selection.
    - **Potential presence of food allergens:** VOWST may contain food allergens as it is manufactured from human fecal matter
- **Adverse reactions**
    - **Common**: abdominal distention, (31%), diarrhea (7%), abdominal distention (4%), flatulence (3%), and nausea (3%)
- **Drug-drug interactions**
    - VOWST contains bacterial spores, therefore antibacterials should not be administered concurrently

Table 2: Safety results from clinical trials

Study	Results
ECOSPOR III	Any ADE related or possibly related to treatment: VOWST 51%, placebo 52% Serious ADE: VOWST 8%, placebo 16% No adverse events were significantly higher with VOWST although there was a numerical different in patients with urinary tract infection (7% vs. 1%). None were related to organisms in VOWST. ADEs more common with placebo included flatulence, abdominal pain, constipation, nausea, vomiting and rCDI
ECOSPOR IV	Treatment emergent ADEs in 54% of subjects. Only UTI was more common with VOWST from the open-label cohort 2 (UTI 6% of subjects vs. none with placebo). None considered related to study drug
ECOSPOR II	AEs occurred in 77% of VOWST and 69% of placebo recipients. SAEs occurred in 10% of VOWST vs. no placebo subjects (severe diarrhea, DVT, drug overdose, abdominal pain x2, and one patient with multiple SAEs). None considered related

Other Considerations

- **Special populations:**
    - **Pregnancy**: There are no data on use of VOWST in pregnant individuals
    - **Lactation:** It is not known whether VOWST is excreted in human milk.
    - **Geriatrics:** Data from clinical trials of VOWST are not sufficient to determine if adults 65 years of age or greater respond differently than younger adults.

- **Supply:**
  - VOWST is supplied as bottles of 12 capsules
- **Procurement:**
  - Details about the ordering process for VOWST in VHA can be found on the Specialty Distribution SharePoint of PBM
  - VOWST can be ordered through Cardinal Specialty health after setting up an account.
- **Storage/stability:**
  - Can be stored at 2°C to 25°C (36°F to 77°F); do not store in the freezer.

Table 3: Other Therapeutic Options

Drug	Formulary status	Clinical Guidance	Other Considerations
Fecal microbiota spore, live (VOWST)	TBD	Approved by FDA for prevention of rCDI in adults following treatment for rCDI No comparative data with other FMT methods, but selection of spores only, and inactivation of live viruses / bacteria may further reduce risk of infectious complications **Guidelines:** Guidelines address FMT in general, not VOWST specifically **IDSA:** FMT recommended if multiple rCDI episodes who have failed standard antibiotics **ACG 2021:** Recommend FMT in patients experiencing 2nd or further recurrence.	Limited safety/efficacy database due to enrollment difficulties Did allow some immunocompromised patients (no data available) While numbers were small, 28% of VOWST and 26% of placebo subjects in ECOSPOR III received fidaxomicin, with a significant reduction in rCDI in that subgroup (4% with VOWST vs. 46% placebo) No data for use with bezlotoxumab Not appropriate for patients requiring continued antibiotic therapy
FMT (REBYOTA)	TBD	Approved by FDA for rCDI in adults Met less stringent but not more stringent posterior probability of superiority over placebo based on 1 phase 3 trial with additional patients borrowed from Phase 2 trial Single enema, which can be administered in multiple healthcare settings (hospital, GI clinic) **Guidelines:** Guidelines address FMT in general, not VOWST specifically **IDSA:** FMT recommended if multiple rCDI episodes who have failed standard antibiotics **ACG 2021:** Recommend FMT in patients experiencing 2nd or further recurrence.	Only a small number of patients received fidaxomicin as SoC; therefore, additional efficacy in reducing relapse with fidaxomicin is unclear Immunocompromised patients not included in clinical trials, and FDA has released several safety communications related to potential for transmission of pathogens No data for use with bezlotoxumab Requires administration by enema and patients must be able to cooperate with procedure Not appropriate for patients requiring continued antibiotic therapy
Bezlotoxumab (ZINPLAVA)	NF	**Approved by FDA in Oct 2016** to reduce recurrence in adults receiving CDI treatment who are at high risk for rCDI -Approval based on 2 DB, PC, Phase 3 RCT which showed 10% reduction in risk of recurrence. -Most patients were in first episode of CDI and > 20% were immunocompromised **Guidelines:** **IDSA 2021:** suggest CDI episode in past 6 months, especially if multiple risk factors **ACG 2021:** consider bezlotoxumab in patients at high risk of recurrence	**Dosing:** 10mg/kg IV once during administration of standard of care (SoC) antibiotics **Other Considerations:** Has been studied in immunocompromised patients Most patients in Phase 3 trials received metronidazole or vancomycin as CDI therapy. Few were on fidaxomicin **Warning:** increased risk of CHF and increased risk of serious adverse events, including death in patients with a history of CHF and should be given only if benefit is felt to outweigh risk

Projected Place in Therapy

- *Clostridioides difficile (C. diff)* causes severe diarrhea and colitis. Within the Veterans Health Administration, there are approximately 10,000 new cases reported per year. Approximately 20% of patients will have rCDI in the following 2-8 weeks and the risk increases with each episode of CDI.

- VOWST is approved as adjunct therapy in patients with rCDI at high risk for recurrence, despite limited data, given the need, seriousness of the condition and lack of approved alternatives. Like bezlotoxumab and REBYOTA, it appears to reduce the risk of rCDI when given after a course of standard CDI therapy, however several differences exist.

- Based on the existing data, and comparison with bezlotoxumab, VOWST may be a useful additional option to reduce risk of rCDI, inpatients with multiple recurrences, in those who cannot use bezlotoxumab (e.g. active CHF or rCDI previously treated with bezlotoxumab). However, in most cases, the overall data are more robust for bezlotoxumab, and would suggest this agent should be tried prior to a trial of FMT unless it is not medically advisable or practicable.

- When selecting an FMT product, VOWST offers several advantages over rectal FMT or unlicensed FMT using local donors or a stool bank. It is administered orally, and due to the inactivation process, may have a lower risk of transmission of pathogens. While the trials for both Rebyota and VOWST are small, the efficacy data with VOWST appeared to be more robust across subgroups. In addition, VOWST goes through an ethanol killing process, eliminating vegetative forms of many microbes, suggesting it MAY be less likely to transmit pathogens with administration.

    - Efficacy, safety, logistics and cost should be considered when choosing between Rebyota and VOWST.

    - **Of note – patients must be able to comply with administration procedures, including pretreatment with a laxative (296 mL of Magnesium citrate, or 250 mL of polyethylene glycol if magnesium citrate cannot be used) and administration on an empty stomach before the first meal of the day**

    - **Importantly, patients who require concomitant antibiotics were excluded from the clinical trials and other antibiotics are likely to reduce the effectiveness of FMT. For those patients who are known or who are likely to need antibiotics in the 8 weeks after VOWST should have other therapy considered (such as continued vancomycin pulse therapy during antibiotic treatment).**

- Given the nuances, ideally specialists such as Infectious Diseases or Gastroenterology providers should be included in the decision to use VOWST, Rebyota or bezlotoxumab for prevention of rCDI to ensure appropriate patient selection and safe use of these products.

- Of note, unlicensed FMT has been studied and use for other gastrointestinal (GI) and non-GI conditions. VOWST is not approved for use other than rCDI. If there is intent to use off-label for additional indications, discussion with the local P&T and local case adjudication should be considered.

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