Fecal microbiota spores, live - jslm (REBYOTA)
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

- REBYOTA (REB) or fecal microbiota live, is a rectal microbiota suspension manufactured from human fecal matter obtained from qualified donors. It was approved by FDA on November 30th, 2022 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. REB was granted Breakthrough therapy, Fast Track and Orphan Drug designations by FDA.
    - Rebyota is not indicated for the treatment of CDI. It is typically administered 24-72 hours after receipt of antibiotic treatment for CDI. Oral antibiotics should be avoided for up to 8 weeks after use.

Dosage Form(s) Under Review

- Rectal enema, suspension: a single 150 mL dose for rectal administration

Clinical Evidence Summary

Efficacy Considerations

- Effectiveness of REB was based on two randomized, double-blind, placebo-controlled trials (DB, PC RCT) in adults with recurrent CDI (rCDI, defined as beginning within 8 weeks after treatment for a primary episode).
- Although two Phase 3 studies were planned, difficulty in enrollment precluded this. As a result, conversations with the FDA resulted in an agreement to complete 1 placebo-controlled phase 3 trial and formally integrate SOME data from the placebo-controlled phase 2 study, through a hierarchical Bayesian analysis that was the PRIMARY ENDPOINT for FDA approval. The two studies are described below:
    - **PUNCH CD2**: phase 2 RCT of **1 or 2 doses of REB versus placebo** in patients with **TWO** or more CDI recurrences after primary episode
        - second dose 7 (+/-2) days after the first but could be earlier if CDI recurred
    - **PUNCH CD3:** phase 3 RCT of a **single dose of REB versus placebo** in patients with **ONE** or more recurrences after primary episode
    - Patients had to have completed at least 10 days of antibiotics for CDI and have their CDI controlled, followed by a washout period of **24-48 hours for CD2** or **24-72 hours for CD3** prior to REB or placebo administration.
- **Bayesian analysis**: during CD3 enrollment, study design was decided to account for difference between studies. **This is the only analysis presented in prescribing information.**
    - Two success thresholds were investigated that represented a posterior probability of superiority (over placebo) of 0.975 or a more stringent threshold of 0.9993 to determine efficacy of REB
- Additional efficacy data are summarized in Table 1.

Table 1: Efficacy Results From Clinical Trials

Reference	Study Design/Intervention	Endpoints	Patient Demographics	Results
Dubberke, 2018, 2023 (Punch CD2)	Randomized, controlled Phase 2b Trial Adults after treatment rCDI (at least 1st recurrence) with CDI symptoms controlled (< 3 loose stools per day) after at least 10 days of CDI antibiotics **Select Exclusions:** history of IBD/ IBS/ celiac / chronic diarrhea, immune compromise, need for concomitant antibiotics Patients randomized 1:1:1 **Group A:** 2 doses REB **Group B:** 2 doses placebo **Group C:** 1 dose REB and 1 dose placebo *2nd dose 7 +/-2 days after first dose**	**Primary Outcome: Treatment success,** defined as absence of CDI without need for retreatment 56 days (8 weeks) after last enema. *Note: Treatment failures eligible for open label REB after retreatment for CDI* -Primary comparison was Group A vs. Group B Primary analysis: ITT*** **Group A**: n=45 **Group B**: n=44 **Group C**: n=44 mITT population **Group A**: n=41 **Group B**: n=44 **Group C**: n=42	**Demographics:**** **Median age** 62-66 yrs. 57-68% female **Median of 3 or 4 prior CDI episodes (range 2-14)** **Vancomycin as CDI treatment** **Group A:** 93% **Group B:** 91% **Group C:** 88% *Fidaxomicin: 1 patient in group A and 2 in Group B and C*	**Efficacy Results: Success** **Group A:** 61% **Group B:** 45% **Group C:** 67% **Primary outcome Group A vs. B in ITT population:** **A:** 61% **B:** 45% P = 0.152, NS **Combined REB groups (A and C) vs. B** **A/C:** 64% **B:** 45% P=0.047 *No difference in efficacy between 1 and 2 doses so 1 dose moved to phase 3 trials* Success at 6 months (ITT): NS different (p=0.2 for 1 dose, 0.24 for 2 doses vs. placebo). mITT, 1 dose but NOT 2 doses superior to placebo
Khanna 2022. (Punch CD3):	Phase 3 DB, PC RCT Inclusion/exclusion as in CD2 except, patients could have **1 or more rCDI episodes (vs. 2 in CD2)** **Intervention:** 2:1 randomization to 1 dose REB or 1 dose placebo enema after a **24-72 hour** washout period at completion of CDI treatment	**Primary endpoint:** Clinical success (absence rCDI within 8 weeks of treatment) **Secondary:** sustained success through 6 months, safety **mITT population:** **REB:** n= 177 **Placebo:** n= 85 *mITT = all treated patients, minus those who withdrew prior to treatment or evaluation for success as long as exit not for CDI symptoms*	**<u>REB vs. placebo</u>** Female: 68% vs. 69% Median age: 64 vs. 60 yrs. **≥65 years of age:** **REB: 49%** **Placebo: 38%** **<u>Vancomycin therapy for CDI episode: 87% vs. 90%</u>** Fidaxomicin: 7% vs. 6% **>3 CDI episodes**, 38% vs. 32% ***Approximately 32% of subjects were treated at first relapse in CD3***	**Treatment success (mITT)** **REB: 71%** **Placebo: 62%** 33% of patients were treated at first recurrence of CDI following antibiotic treatment of CDI REBYOTA demonstrated a statistically significant 70.5% (126/177) treatment success at 8 weeks vs placebo at 57.5% (53/85) Of the patients who saw success, 92% (116/126) had a sustained response through 6 months. Placebo was 91% (48/53)
FDA Bayesian	Bayesian analysis using dynamically borrowed	Primary outcome of clinical success (no rCDI	After aligning the analysis populations from PUNCH	**Treatment success in borrowed PUNCH CD2 mITT population:**

analysis (PUNCH CD2 and 3)	information about treatment effect from PUNCH CD2, using only the 1 dose REB group and placebo group. As definitions for mITT and ITT were different between studies, the PUNCH CD3 definitions were reapplied to "borrowed" patients from PUNCH CD2 ***Of note – differences did exist in number of prior rCDI episodes allowed and washout period***	to 8 weeks post-treatment) was applied to combined population with mITT population as primary analysis population Combined data used to identify posterior probability of superiority at 2 thresholds: >0.999 and a less stringent > 0.975	CD2: 39 and 43 subjects were added to the REB and placebo populations, respectively Total combined analysis populations: mITT: REB: n=177 Placebo: n= 85 ITT: REB: n = 180 Placebo: n = 87 *Note: 41 REB (23%) and 24 placebo (28%) patients were designated as failures and received an open-label dose of REB*	**REB:** 64% (25/39) **Placebo:** 44% (19/43) **Treatment success from combined CD2 + CD3 (mITT):** **REB: 71%** **Placebo: 57%** **Mean treatment effect:** 13% **95% credible interval** (2%, 24%) **Posterior probability of superiority:** 0.991 **REB met the second success threshold (posterior probability 0.975) but did NOT meet the more stringent success threshold (0.9993)** Analysis in the ITT population found similar results 90% of both groups with treatment success had sustained response at 6 months

**second dose could be given sooner if CDI recurred in less than 7 days. **demographics are reported as a range across the groups ***ITT population = all patients randomized, mITT = all patients randomized who received at least one dose*

Efficacy summary:

- REB was designated as a breakthrough therapy, and orphan drug by the FDA, suggesting an unmet medical need (previously met through unregulated FMT). Due to low enrollment due to FDA's decision to use enforcement discretion on unregulated FMT products, they worked with the manufacturer to identify a different analysis plan – allowing for one phase 3 trial, and borrowing patients from the single-dose arm of the blinded phase 2 trial
- Treatment success was numerically higher with REB (from 9-13% depending on trial population) but did not meet criteria for statistical superiority
- In the combined, Bayesian analysis of REB vs. placebo after treatment for an episode of rCDI, REB met the less stringent, but not more stringent threshold for posterior probability of success, with an absolute difference in 8 week clinical success of 13%
    - A significant proportion of patients in both groups received unblinded, open-label REB due to perceived clinical failure by the treating investigator
- Based on the above results, FDA approved the use of REB for adults with rCDI

Safety Considerations

- REB is a fecal microbiota suspension manufactured from human fecal matter sourced from qualified donors, and is tested for a panel of transmissible pathogens. FDA outlined a very strict requirement of pathogens and testing schedule for donors. Safety data comes from PUNCH CD2 and CD3 as well as 3 additional open-label phase 2 and 3 studies

- Safety data comes from 978 adults who received one or more doses of REB in either of the 2 RCTs, or from 3 additional open-label studies

- **Contraindications:** Severe allergic reactions (e.g. anaphylaxis) to any component of REB
- **Other warnings / precautions**:
    - **Transmissible infectious agents**: REB carries risk for transmitting infectious agents as it is manufactured from human fecal matter
        - Of note, patients with immune compromise, including those on corticosteroids (≥ 20mg/day prednisone or equivalent), those with an absolute neutrophil count < 1000 cells/uL or other conditions or therapies that caused a compromised immune system
        - 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.
    - **Management of acute allergic reactions:** Following administration of REB, appropriate treatment must be available in the event of a potential anaphylactic reaction
    - **Potential presence of food allergens:** REB may contain food allergens as it is manufactured from human fecal matter
- **Adverse reactions**
    - **Common**: abdominal pain, (8.9%), diarrhea (7.2%), abdominal distention (3.9%), flatulence (3.3%), and nausea (3.3%)

Table 2: Safety results from clinical trials

Study	Results
Dubberke, et al. 2018 (Punch CD2)	PUNCH CD2 evaluated a 2 doses of REB (Group A), placebo (Group B) and 1 dose of REB (Group C) *All subjects could receive up to 2 additional open label doses for a total of 1-4 doses possible* Treatment discontinuation – and number due to death **Group A:** 14/45 (31%) – death in 8/14 **Group B:** 9/44 (20%) – death in 2/9 **Group C:** 19/44 (43%) – death 6/44 *-Of the 16 deaths reported, 1 was due to severe CDI complications prior to receipt of the dose. The other 15 subjects died a median of 281 days (range 57-670 days) after the first enema. All has plausible alternate etiologies and were not considered related to REB by the FDA reviewers.* Definitely, probably or possibly related adverse events (AE) in ≥3% REB subjects and rate greater than placebo: Group A: 17% (7% TEAEs related to REB) Group B: 9% (0 considered related to REB) Group C: 13% (0 considered related to REB)
Khanna et al. 2022. (Punch CD3)	higher rate of adverse events (AEs) reported in the REB group (56%) compared with the placebo group (45%), but similar rate of moderate/severe AEs. Most occurred in the first 2 weeks after treatment. Deaths: 2 with REB vs. 0 with placebo but neither deemed related to treatment **Definitely, probably or possibly related AE in ≥3% REB subjects and rate greater than placebo:** **Abdominal pain**: 9% REB vs. 7% placebo **Diarrhea**: 7% REB vs. 3% placebo **Abdominal distension**: 4% REB vs. 2% placebo **Flatulence**: 3% REB vs. 0 placebo **Nausea**: 3% REB vs. 1% placebo

Other Considerations

- **Special populations:**

  - **Pregnancy**: following rectal administration, REB is not absorbed systemically, and maternal use is not expected to result in fetal exposure to the drug.
  - **Lactation:** breastfeeding is not expected to result in exposure of the child to REB
  - **Geriatrics:** data from clinical trials of REB are not sufficient to determine if adults 65 years of age or greater respond differently than younger adults.

- **Supply:**
  - REB is shipped together in a box with the administration set.
  - Each box may contain up to 6 cartons of REB and up to 6 administration sets.
  - Each carton of REB contains a single dose for rectal administration.

- **Storage/stability:**
  - Upon receipt, store carton in an ultracold freezer (−60°C to −90°C [−76°F to −130°F]).
  - Alternatively, may store refrigerated at 2°C to 8°C (36°F to 46°F) for up to 5 days (including thaw time); do not refreeze.
  - Store administration set separately at 10°C to 34°C (50°F to 93°F); do not store in the freezer.
- **Administration:**
  - REBYOTA is administered rectally as an enema

Other Therapeutic Options

Alternative treatments for CDI are listed in table 3 below

Table 3: Treatment Alternatives

Drug	Formulary status	Clinical Guidance	Other Considerations
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 **Guidelines:** Guidelines address FMT in general, not REB specifically **IDSA:** FMT recommended if multiple rCDI episodes who have failed standard antibiotics **ACG 2021:** suggest FMT be considered with severe and fulminant CDI refractory to therapy and are poor surgical candidate. Recommend FMT in patients experiencing 2nd or further recurrence. Recommend delivery through colonoscopy and suggest repeat FMT if additional recurrence within 8 weeks	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 combining with bezlotoxumab or other therapies to reduce the risk of relapse Requires administration by enema and patients must be able to cooperate with procedure REB not studied for other situations where FMT used, such as IBD, IBS or non-GI disorders.
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 rCDI -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

COMPARISON: BEZLO vs. FMT	Pooled Data: MODIFY 1 and II		Punch CD3	
Characteristic N (%)	Bezlotoxumab (N=781)	Placebo (N=773)	RBX2660 (n=180)	Placebo (n=87)
Metronidazole for CDI	379 (48.5)	374 (48.4)	----	----
Vancomycin for CDI	372 (47.6)	373 (48.3)	157 (87.2)	78 (89.7)
Fidaxomicin for CDI	30 (3.8)	26 (3.4)	12 (6.7)	5 (5.7)
Vancomycin + metro OR fidaxomicin	-----	-----	5 (2.8)	2 (2.3)
Other (various other antibiotics alone or in combination)	-----	-----	6 (3.3)	2 (2.3)
≥ 1 previous CDI episode in past 6 months	216 (27.7)	219 (28.3)	-----	-----
≥ 2 previous CDI episodes ever	100 (12.8)	126 (16.3)		
≤3 CDI episodes before blinded treatment	-----	-----	111 (61.7)	59 (67.8)
3 CDI episodes before blinded treatment	-----	-----	69 (38.3)	28 (32.2)

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.
- REB is manufactured from human fecal matter sourced from qualified donors. While unlicensed FMT preparations continue to be used, FDA has previously stated it will use discretion (i.e. not take action) when used. REB offers the first FDA approved product and it is unclear what will happen now that an approved product is available.
- REB is approved as adjunct therapy in patients with rCDI at high risk for recurrence, despite limited data, given need, seriousness of the condition and lack of approval alternatives. Like bezlotoxumab, it appears to reduce the risk of rCDI by about 10-13% when given after a course of standard CDI therapy, however several differences exist.
    - Bezlotoxumab was used earlier – ¾ of patients had not had a previous episode of CDI in the prior 6 mo. All patients with REB had had at least 1 recurrence by 8 weeks after a prior episode.
    - Bezlotoxumab is given as an intravenous infusion and can be given at any point during treatment, while REB must be given 24-72 hours after completion of therapy
    - Approximately half of patients received metronidazole with bezlotoxumab, while nearly 90% of patients received vancomycin as primary therapy with REB. Very few patients received fidaxomicin as primary therapy with either product and it is unclear the degree of additional reduction of rCDI seen when they are used with fidaxomicin.
    - The role of other therapies (e.g. fidaxomicin extended regimen, vancomycin taper/pulse, or vancomycin with rifaximin) for prevention of rCDI is less well defined.
    - Bezlotoxumab has a warning to use in patients with CHF only if the benefits outweigh risks, while REB does not
    - Significant numbers of patients in the bezlotoxumab trials were immunosuppressed (25%) while this was an exclusion to the REB trials, and there is concern/potential for pathogen transmission.
    - Bezlotoxumab has several years of additional post-marketing safety, and numerous real-world and subgroup analyses supporting benefit, particularly in patients with several risk factors for rCDI. While many real-world and a few RCTs support FMT, the product, delivery, administration and regimen are uncontrolled and use unapproved licensed products.
- Based on the existing data, and comparison with bezlotoxumab, REB may be a useful additional option to reduce risk of rCDI, in patients with multiple recurrences, and those who cannot use bezlotoxumab (e.g. active CHF). 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.
- The role of either agent when the primary antibiotic therapy used is fidaxomicin is unclear, particularly in patients on a first recurrence or those who are at lower risk for rCDI.
- Given the nuances, ideally specialists such as Infectious Diseases or Gastroenterology providers should be included in the decision to use REB 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. REB 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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