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## Reimbursement Recommendation

# Fecal Microbiota (Rebyota)

**Indication:** For the prevention of recurrence of *Clostridioides difficile* infection (CDI) in adults following antibiotic treatment for recurrent CDI

**Sponsor:** Ferring Canada Inc.

**Final recommendation:** Reimburse with conditions

# Summary

## What Is the Reimbursement Recommendation for Rebyota?

Canada's Drug Agency (CDA-AMC) recommends that Rebyota be reimbursed by public drug plans for the prevention of recurrence of *Clostridioides difficile* infection (CDI) in adults if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Rebyota should only be covered for adult patients who have experienced 2 or more recurrences of CDI despite appropriate antibiotic treatment for previous episodes. Rebyota is administered after completing antibiotic therapy for the current CDI recurrence.

### What Are the Conditions for Reimbursement?

Rebyota should only be reimbursed if prescribed and administered by doctors and care teams who are experienced in treating repeat CDI and in using this type of treatment, and if the cost of Rebyota is reduced. Rebyota should only be reimbursed as 1 dose. If CDI comes back after that first dose, patients may be able to get another dose for each recurrence, if the original initiation criteria are met.

### Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that Rebyota likely resulted in a clinically important increase in treatment success rate over 8 weeks compared to placebo to prevent recurrence of CDI in adult patients. At the 6-month follow-up, a sustained clinical response was observed in most patients who had initially responded at 8 weeks.
- Based on the CDA-AMC assessment of the health economic evidence, Rebyota does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Patients expressed a need for treatments that are symptom-relieving, curative, and preventive of CDI recurrences. Rebyota may help address the important unmet need by improving access to fecal microbiota therapy for the prevention of recurrent CDI (rCDI).
- Based on public list prices, Rebyota is estimated to cost the public drug plans approximately $40 million over the next 3 years. However, the actual budget impact is uncertain.

# Summary

## Additional Information

### What Is CDI?

*Clostridioides difficile* colonizes the gut, leading to profuse watery diarrhea that can escalate to fulminant colitis with systemic toxicity and shock. The projected number of CDI cases in Canada in 2024 was approximately 47,000. Patients emphasized the substantial burden of CDI on mental health, daily life, and overall well-being. Symptoms include fatigue, weight loss, abdominal pain, frequent and urgent bathroom use, alongside psychological distress due to anxiety, depression, and social isolation.

### Unmet Needs in rCDI

Despite the availability of conventional fecal microbiota transplant, access remains limited due to several logistical and infrastructural barriers. The current system does not adequately meet patient needs, and there is a need for more standardized, scalable, and accessible treatment options for rCDI in Canada.

### How Much Does Rebyota Cost?

Treatment with Rebyota is expected to cost $9,125 per patient per treatment course.

## Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that fecal microbiota (Rebyota) be reimbursed for the prevention of recurrence of CDI in adults following antibiotic treatment for rCDI only if the conditions listed in Table 1 are met.

## Rationale for the Recommendation

Evidence from 1 phase III, multicentre, double-blind, randomized controlled trial (RCT) (PUNCH CD3) demonstrated that treatment with a single dose of fecal microbiota (Rebyota) likely resulted in a clinically important increase in treatment success rate over 8 weeks compared to placebo to prevent recurrence of CDI in adult patients with a between-group difference of 12.3% (95% credible interval [CrI], 1.4 to 23.3). The clinical experts noted that the point estimate suggests a meaningful benefit for patients despite the uncertainty associated with the wide CrI. At the 6-month follow-up, a sustained clinical response was observed in most patients who had initially responded at 8 weeks, regardless of whether they received fecal microbiota (Rebyota) or placebo. Results for health-related quality of life (HRQoL) suggested little to no clinically important difference between the fecal microbiota (Rebyota) and placebo treatment groups at 8 weeks, based on the *Clostridioides difficile* Quality of Life Survey (Cdiff32); however, the PUNCH CD3 trial was not designed to assess these outcomes, and the clinical relevance of the estimated minimum clinically important difference (MCID) remains uncertain. Efficacy results from the PUNCH CD2 trial and the single-arm PUNCH OLS study showed treatment success at 8 weeks, consistent with the results of the PUNCH CD3 trial.

As the PUNCH CD3 trial included a placebo control group, there is no direct evidence to inform the comparative effectiveness and safety of fecal microbiota (Rebyota) relative to other currently used therapies for the prevention of rCDI, particularly conventional multidose fecal microbiota transplant (FMT) and prolonged vancomycin taper or pulse regimens.

Patients emphasized the chronic nature of CDI and substantial burden on mental health, daily life, and overall well-being. They expressed a desire for treatments that are symptom-relieving, curative, and preventive of CDI recurrences. CDEC acknowledged that conventional FMT is difficult for patients to access. Therefore, while recognizing the limitations in the submitted evidence, CDEC considered this current inequity and concluded that fecal microbiota (Rebyota) may help address an important unmet need by improving access to fecal microbiota therapy for the prevention of rCDI.

The committee considered the base-case analysis presented by CDA-AMC alongside the scenario analyses and uncertainties presented. The analysis considered most appropriate by CDEC was aligned with submitted data and consisted of a combination of scenario analyses conducted in the CDA-AMC Pharmacoeconomic Review report that removed all assumptions leading to a mortality and colectomy benefit associated with fecal microbiota (Rebyota), assumed there was no difference in sustained response with fecal microbiota (Rebyota), and permitted patients to be retreated with fecal microbiota (Rebyota) upon recurrence. The committee felt this aligned more closely with the available clinical data and CDEC recommendation. Using

the sponsor-submitted price for fecal microbiota (Rebyota) and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for fecal microbiota (Rebyota) considered most appropriate by CDEC was therefore $802,187 per quality-adjusted life-year (QALY) compared with no preventive therapy (health care payer perspective). At this ICER, fecal microbiota (Rebyota) is not cost-effective at a $50,000 per QALY willingness to pay threshold for the prevention of recurrence of CDI in adults following antibiotic treatment for rCDI. A price reduction is required for fecal microbiota (Rebyota) to be considered cost-effective at a $50,000 per QALY threshold.

## Table 1: Reimbursement Conditions and Reasons

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| **Initiation** | | |
| 1. Adult patients who have experienced at least 2 recurrences of CDI despite appropriate antibiotic treatment for rCDI. | The evidence from the PUNCH CD3 trial identifies a benefit in recurrence for patients receiving a single dose of fecal microbiota (Rebyota) vs. placebo. In addition, 68% of patients who received fecal microbiota (Rebyota) in the PUNCH CD3 trial had at least 2 recurrences before receiving fecal microbiota (Rebyota).<br>The clinical experts noted to CDEC that patients with the greatest unmet need are those who have experienced at least 2 CDI recurrences; at least 1 of which happened despite an appropriate antibiotic treatment consisting of a prolonged vancomycin taper or pulse regimen. | To be eligible for enrolment in the PUNCH CD3 trial, patients were required to either be currently receiving or have been newly prescribed antibiotics for the management of CDI-related diarrhea at the time of enrolment. Additionally, a positive stool test confirming the presence of toxigenic *Clostridioides difficile* within the preceding 30 days was required.<br>For the treatment of a second or subsequent recurrence of CDI, the antibiotic treatment recommended by the AMMI Canadian Guidelines is vancomycin administered using a tapering and/or pulsed dosing regimen. |
| **Prescribing** | | |
| 2. Reimbursement for fecal microbiota (Rebyota) should be limited to a single initial dose. In the case of a CDI recurrence after the first dose, an additional single dose may be eligible for reimbursement per recurrence, provided that the original initiation criteria remain applicable. | In the PUNCH CD3 trial, patients received a single dose of fecal microbiota (Rebyota). Patients who had a CDI recurrence could receive an additional, open-label fecal microbiota (Rebyota) enema. | Clinical experts noted to CDEC that if CDI recurs following fecal microbiota (Rebyota) treatment, an appropriate antibiotic treatment should be initiated before readministering fecal microbiota (Rebyota).<br>Recurrence of CDI in the PUNCH CD3 trial was defined as the presence of CDI diarrhea, with a positive stool test for the presence of *Clostridioides difficile* toxin, within 8 weeks of administration of a study enema. |
| 3. Prescribing and treatment administration of fecal microbiota (Rebyota) should be limited to clinicians and health care teams with expertise in the management of patients with rCDI and the administration of fecal microbiota (Rebyota). | This will allow optimization of the selection of patients who may benefit the most from treatment with fecal microbiota (Rebyota).<br>The experts emphasized that fecal microbiota (Rebyota) is not risk-free and that providers should be aware of the risks and alternatives in discussing treatment options with patients. | — |

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| **Pricing** | | |
| 4. A reduction in price. | The ICER for fecal microbiota (Rebyota) is $802,187 per QALY gained when compared with no preventive therapy (health care payer perspective). This analysis removed all mortality and colectomy benefit associated with fecal microbiota (Rebyota), assumed there was no difference in sustained response with fecal microbiota (Rebyota) and permitted patients to be retreated with fecal microbiota (Rebyota) upon recurrence. Based on this scenario, a price reduction of 87% would be for fecal microbiota (Rebyota) required to achieve an ICER of less than $50,000 per QALY gained compared with no preventive therapy. | — |
| **Feasibility of adoption** | | |
| 5. The feasibility of adoption of fecal microbiota (Rebyota) must be addressed. | At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and the CDA-AMC estimates. | — |

AMMI = Association of Medical Microbiology and Infectious Disease; CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; CDI = *Clostridioides difficile* infection; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; rCDI = recurrent *Clostridioides difficile* infection; vs. = versus.

## Discussion Points

- **Reconsideration request:** The sponsor requested a reconsideration of the initial draft recommendation to not reimburse fecal microbiota (Rebyota) for the prevention of recurrence of CDI in adults following antibiotic treatment for rCDI. There were 3 issues outlined by the sponsor in the request for reconsideration that were discussed by CDEC. The sponsor expressed concerns regarding the interpretation of the findings; in their view, the overall evidence is suggestive of clinically meaningful effectiveness. The sponsor also highlighted the unmet needs in this condition, suggesting that the limitations of conventional FMT have not been fully acknowledged. They also noted that conducting indirect treatment comparisons (ITCs) with other therapies was not feasible. Finally, the sponsor argued that patients included in the studies were representative of those seen in clinical practice in Canada, especially regarding the antibiotic treatment received for the qualifying episode and the prior number of recurrences.
- **Unmet need:** During the initial and reconsideration meetings, CDEC discussed input from patient groups that emphasized the need for accessible treatment options that can effectively prevent CDI recurrence. The committee acknowledged growing evidence suggesting that FMT may help address this need following antibiotic treatment of active infection. In Canada, FMT is regulated as a biologic

drug and is subject to the same stringent requirements as other biologic drugs. Although commercial FMT products are not yet available, conventional FMT has been permitted since 2015 under Health Canada policy guidance. However, access to conventional FMT remains limited due to several logistical and infrastructural barriers. CDEC acknowledged that despite the availability of conventional FMT, the current system does not adequately meet patient needs, and that there is a need for more standardized, scalable, and accessible treatment options for rCDI in Canada. During the reconsideration meeting, CDEC acknowledged the feedback received from the clinician and patient groups and balanced uncertainties in the evidence against the unmet needs.

- **Access to conventional FMT:** During the initial and reconsideration meetings, CDEC acknowledged that access to conventional FMT remains limited due to several logistical and infrastructural barriers. These include challenges in identifying and screening suitable donors, a lack of trained personnel, and the absence of standardized infrastructure. CDEC noted that while conventional FMT is an effective treatment, these access barriers create a fragmented and inconsistent landscape. Clinical experts emphasized that the lack of public or private funding forces FMT programs to rely heavily on local programs led by individual physicians. Additionally, establishing and maintaining stool banks is difficult due to strict donor eligibility criteria and the voluntary nature of donation, which makes donor retention challenging. During the reconsideration meeting, CDEC acknowledged the feedback received from the clinician and patient groups who emphasized that fecal microbiota (Rebyota) may offer a more standardized and accessible alternative to conventional FMT.
- **Patient and clinician group feedback on the draft recommendation:** During the reconsideration meeting, CDEC reviewed feedback on the draft recommendation from 3 patient groups and 8 clinician groups and acknowledged the unmet therapeutic need in the management of rCDI. The feedback emphasized the potentially chronic nature of CDI and substantial burden on mental health, daily life, and overall well-being. Patient groups expressed a desire for treatments that are symptom-relieving, curative, and preventive of CDI recurrences. Clinicians emphasized that fecal microbiota (Rebyota) may address an important unmet need by improving access to fecal microbiota therapy, especially considering the limited access to conventional FMT in Canada. During the reconsideration meeting, CDEC recognized the perspectives and experiences of the clinician groups and individual clinicians who treat CDI recurrences, particularly with respect to the perceived efficacy of fecal microbiota (Rebyota), as well as the limitations seen with other treatment options. The clinicians noted that long-term antibiotics are associated with high treatment cost, negative effects on the intestine microbiome, and increased risk of resistance. They also noted that conventional FMT is difficult for patients to access and that practitioners are faced with challenges in establishing and maintaining FMT programs.
- **Efficacy and certainty of evidence:** During the initial and reconsideration meetings, CDEC discussed the clinical efficacy of treatment, noting that in the PUNCH CD3 trial, fecal microbiota (Rebyota) likely resulted in a clinically important increase in treatment success rate at 8 weeks compared to placebo (70% versus 58%; 12.3% difference) with moderate certainty. The CrI around the primary end point was wide (95% CrI, 1.4 to 23.3), adding uncertainty to the results; however,

the clinical experts confirmed that the point estimate suggests a meaningful benefit for patients. CDEC noted that in the in PUNCH CD3 trial, at the 6-month follow-up, a sustained clinical response was observed in most patients who had initially responded at 8 weeks, regardless of whether they received fecal microbiota (Rebyota) or placebo (92.1% versus 90.6%); during the reconsideration meeting, CDEC discussed that the absence of recurrence in the long-term may be driven by the natural history of early success. Based on results from exploratory analyses, fecal microbiota (Rebyota) may result in little to no difference in HRQoL, as measured with the Cdiff32, over 8 weeks compared to placebo; however, the PUNCH CD3 trial was not designed to assess these outcomes. HRQoL results at 6 months were too uncertain to draw a definite conclusion. CDEC noted that the uncertainty regarding the generalizability of the patient population who were enrolled, long-term efficacy, and the HRQoL improvement limits conclusions about its broader impact on efficacy outcomes. However, during the reconsideration meeting, CDEC deemed that the 8-week data were more relevant for assessment of CDI recurrences, where fecal microbiota (Rebyota) likely results in a clinically important increase in the treatment success rate compared to placebo. CDEC also noted that fecal microbiota (Rebyota) was not directly or indirectly compared to conventional FMT but acknowledged that the absence of such comparison may not preclude a reimbursement recommendation.

- **Prior vancomycin treatment:** In the PUNCH CD3 trial, although the majority of patients received vancomycin for the treatment of the qualifying episode, no details were reported regarding the specific regimen used (e.g., whether patients received a prolonged taper or pulse vancomycin treatment as per the recommendations from the Canadian guidelines). However, during the reconsideration meeting, CDEC acknowledged that there is no taper regimen that is considered standard of care (SOC), and that clinicians use their judgment in terms of antibiotic dosage and treatment duration. This results in high variability in terms of the taper or pulse regimens used across patients. Therefore, CDEC concluded that despite uncertainties, the use of placebo as a comparator may be acceptable.
- **Place in therapy:** The clinical experts noted to CDEC that patients included in the trial were likely at a lower risk of experiencing CDI recurrences than patients typically seen in clinical practice who would be the best candidates to receive fecal microbiota (Rebyota), one of the reasons being the inclusion of patients who had only 1 recurrence of CDI, who accounted for 29.5% of patients in the fecal microbiota (Rebyota) group and 38.5% of patients in the placebo group. Patients who experience a first recurrence may have their condition improve spontaneously and maintain a sustained response without active treatment. However, the natural disease trajectory becomes more severe in patients who have experienced at least 2 recurrences, and the risk of experiencing further recurrences becomes incrementally higher. Therefore, the clinical experts emphasized that fecal microbiota (Rebyota) should be reserved for patients who have experienced at least 2 CDI recurrences, at least one of which happened despite an appropriate antibiotic treatment consisting of a prolonged vancomycin taper or pulse regimen. This place in therapy for fecal microbiota (Rebyota) is consistent with that of conventional FMT in the Association of Medical Microbiology and Infectious Disease Canada practice guidelines for CDI.

- **Additional studies:** CDEC discussed the additional studies reviewed to address gaps in the evidence, with results from the PUNCH CD2 trial and the single-arm PUNCH OLS study generally aligning with those of the pivotal PUNCH CD3 trial, supporting short-term treatment efficacy at 8 weeks. However, in the PUNCH CD2 trial the primary outcome's null hypothesis between group A and group B was not rejected, and the single-arm PUNCH OLS study lacked a randomized comparator, limiting causal conclusions. Real-world findings by Feuerstadt et al. also suggest similar treatment success in patients with comorbidities, providing supportive evidence of effectiveness in broader clinical populations. CDEC noted that the study by Feuerstadt et al. is similarly limited by its open-label study design and the use of more doses than recommended by Health Canada, which may overestimate efficacy.
- **Harms:** CDEC discussed the safety profile of fecal microbiota (Rebyota) which did not raise any safety signals among for the clinical experts consulted. However, the clinical experts indicated that there may be long-term, unintended effects of manipulating a patient's microbiome, such as affecting the risk of developing a range of conditions over time, the impact of which is currently unknown. While no major harms were definitively reported in the PUNCH CD3 trial, 4 patients in the treatment group required hospitalization compared to none in the placebo group. CDEC discussed the use of fecal microbiota (Rebyota) in patients who were immunocompromised and who were excluded from the PUNCH CD3 trial. CDEC noted that in consultation with the clinical experts, caution is advised when administering fecal microbiota (Rebyota) to patients with severe immunocompromising conditions; however, the clinical experts did not view this as a contraindication to its use.
- **Economic considerations:** CDEC identified substantial uncertainty in the analysis of cost-effectiveness of fecal microbiota (Rebyota) due to a lack of comparative data to support a benefit in terms of mortality and colectomy rates and maintained differences in sustained response between fecal microbiota (Rebyota) and no preventive therapy. CDEC therefore considered that the CDA-AMC base case likely overestimated the benefit of fecal microbiota (Rebyota). As well, CDEC's recommendation supported providing a further dose of fecal microbiota (Rebyota) upon subsequent recurrence (aligned with the Health Canada product monograph), which did not align with the CDA-AMC base-case analysis. Given this uncertainty, CDEC considered a combination of the scenario analyses conducted by CDA-AMC to be more reflective of the evidence and recommendation. This scenario mitigates the influence of benefit for fecal microbiota (Rebyota) that has not been clinically proven, resulting in an ICER of $802,187 per QALY gained compared with no preventive therapy.
- **Budget impact analysis:** In the CDA-AMC budget impact analysis, patients were only treated with 1 dose of fecal microbiota (Rebyota), This does not align with the Health Canada product monograph, which permits a subsequent dose of fecal microbiota (Rebyota) upon recurrence. As such, the budget impact of reimbursing fecal microbiota (Rebyota) for CDI may be underestimated in the CDA-AMC base case.
- **Societal perspective:** CDEC discussed the sponsor's societal perspective analysis, which included indirect costs such as productivity loss and travel costs. CDEC noted that indirect costs were

not assessed in the PUNCH trials and that the evidence submitted by the sponsor to support the estimated impact of fecal microbiota (Rebyota) on indirect costs was uncertain. Due to the uncertainty in evidence of the impact of fecal microbiota (Rebyota) on indirect costs, the committee deemed that the results of this analysis were too uncertain to inform decision-making.

- **Storing fecal microbiota (Rebyota):** CDEC discussed that fecal microbiota (Rebyota) needs to be kept frozen in an ultracold freezer at −60°C to −90°C (until its expiration) or in a regular refrigerator for up to 5 days (including the 24-hour thawing period). The sponsor noted that a patient support program will be offered to dispensing pharmacies. Fecal microbiota (Rebyota) and ancillary supplies (i.e., administration kit) will be shipped with validated cold chain packaging for just in time delivery to the administration site.
- **Equity of access:** CDEC discussed several barriers that may impact equitable access to fecal microbiota (Rebyota), including health system capacity, geography, and mode of administration. Because fecal microbiota (Rebyota) is expected to be administered in specialized settings, individuals in rural or remote locations may face greater challenges in accessing care, with increased costs to the medical system and to patients. CDEC acknowledged that while geographic barriers are not unique to the use of fecal microbiota (Rebyota), they reflect broader challenges in the delivery of specialized treatments that are nonetheless significant. In addition, the enema-only formulation may pose barriers. The committee suggested that these inequities in access could be addressed through a multilevel approach. This may include enhancing supportive care pathways (e.g., referral and follow-up processes), considering alternative modes of administration, and exploring system-level strategies such as expanding service availability.

## Background

CDI is a spore-forming, toxin-producing, gram-positive anaerobe that colonizes the gut, frequently in association with antibiotic therapy. Its hallmark symptom is profuse watery diarrhea (≥ 3 loose stools in 24 hours), although severity ranges from mild diarrhea to fulminant colitis with systemic toxicity and shock. CDI is a leading cause of health care-associated diarrhea, contributing to significant morbidity and mortality. rCDI occurs when symptoms return, often within 2 to 8 weeks posttreatment, affecting up to 25% of patients within 30 days. Diagnosis is based on clinical presentation and stool testing. CDI significantly impacts HRQoL, affecting physical, mental, social, and professional functioning. Patients report symptoms like fatigue, weight loss, abdominal pain, and frequent, urgent bathroom use, alongside psychological distress, including anxiety, depression, and social isolation.

The projected number of CDI cases in Canada in 2024 was approximately 47,000. In Canada, health care-associated CDI rates (CDI that has been acquired in a health care facility) were 3.54 infections per 10,000 patient days in 2021. CDI severity increases with age, as seen in a 2002 Quebec outbreak where infection rates were 10 times higher in patients aged 65 years or older than in younger patients. CDI is associated with a substantial increase in the risk of mortality with reported 30-day all-cause mortality rates ranging from 6.1% in Germany to 11.4% in the US. In Canada, the mortality rate within 30 days of CDI diagnosis in

2021 was 2.3 per 100 cases. The Health Canada–approved indication for fecal microbiota (Rebyota) is for the prevention of recurrence of CDI in adults following antibiotic treatment for rCDI which is in line with the sponsor's reimbursement request. To note, the sponsor requests reimbursement to prevent rCDI as early as the first recurrence. The recommended dose of fecal microbiota (Rebyota) is 1 single dose of 150 mL microbiota suspension by rectal administration. Additional treatment may be administered in the event of CDI recurrence.

## Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III RCT in patients aged 18 years or older with rCDI (PUNCH CD3); 1 phase II RCT in patients aged 18 years or older with rCDI (PUNCH CD2); 1 phase III prospective open-label study in patients aged 18 years or older with rCDI including patients with irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and immunocompromised conditions (PUNCH OLS); 1 retrospective, open-label single-arm study in patients aged 18 years and older with rCDI including patients with IBS, IBD, and immunocompromised conditions (Feuerstadt et al.); and 1 integrated safety analysis pooling data from 5 prospective studies (Lee et al.)
- patients' perspectives gathered by 3 patient groups: the GI Society, the Peggy Lillis Foundation, and the Canadian Digestive Health Foundation
- input from public drug plans that participate in the reimbursement review process
- 3 clinical specialists with expertise diagnosing and treating patients with CDI
- input from 1 clinician group: the Canadian Antimicrobial Resistance Alliance
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to fecal microbiota (Rebyota)
- information submitted as part of the sponsor's request for reconsideration (described subsequently)
- feedback on the draft recommendation.

## Perspectives of Patients, Clinicians, and Drug Programs

### Patient Input

Patient input was submitted by the GI Society, the Peggy Lillis Foundation, and the Canadian Digestive Health Foundation for this review with data gathered from patient questionnaires, interviews, social media posts, emails, and personal stories. The total number of patients who contributed to the input was not reported. According to the input, CDI is a debilitating condition characterized primarily by severe diarrhea, often accompanied by symptoms like dehydration, fever, abdominal pain, and fatigue. It can lead to life-threatening complications, including recurrent infections, sepsis, and, in extreme cases, the need for

colon removal. Certain populations, such as those aged 65 years or older or individuals taking prolonged antibiotics, are at higher risk. The input noted that with the chronic nature and high recurrence rate, the impact of CDI extends beyond physical symptoms, profoundly affecting patients' mental health with feelings of shame, anxiety, and even posttraumatic stress disorder. The condition disrupts daily life, requiring isolation to prevent transmission and placing significant burdens on patients, caregivers, and their ability to work or socialize.

The patient input stated that current treatments for CDI include antibiotics like vancomycin, metronidazole, and fidaxomicin. However, metronidazole has limited effectiveness for severe cases and has significant side effects. Despite these advancements, the input noted that such treatments can destabilize gut microbiota, contributing to the cycle of recurrence. The input stated that probiotics and prebiotics may be helpful in improving the balance of the microbiome, but current research has not yet provided evidence of their benefit in CDI management. As such, the input notes that there is need for treatments that adequately manage symptoms, are curative, and prevent CDI recurrence.

Patients who had experience with the treatment under review reported significant benefits, citing ease of access, minimal side effects, and effective relief from rCDI. Many wish it were offered earlier in their treatment journey. Among the respondents, fecal microbiota (Rebyota) was preferred versus vancomycin due to its simpler administration — delivered once via enema or colonoscopy without the need for bowel preparation — and its ability to address microbiome dysbiosis, reducing vulnerability to future recurrences. Patients highlighted its simplicity and efficiency, with the procedure taking about 30 minutes and causing only minor side effects such as slight cramping.

## Clinician Input

### Input From Clinical Experts Consulted for This Review

The clinical experts highlighted that there is a need for accessible, effective, and well-tolerated therapies to prevent rCDI in patients who have a multirecurrent condition despite appropriate antibiotic treatment, and who have a substantially impacted quality of life from the condition. As such, the clinical experts recommended the use of fecal microbiota (Rebyota) in patients who have experienced at least 2 recurrences, at least 1 of which happened despite a prolonged vancomycin taper or pulse regimen. Patients who experience a first recurrence may have their condition improve spontaneously. However, the natural disease trajectory becomes more complex in patients who have experienced at least 2 recurrences, and the risk of experiencing further recurrences becomes incrementally higher. The clinical experts expect that fecal microbiota (Rebyota) would be used in clinical practice in patients who have concomitant IBD or immunocompromising conditions despite that these populations were underrepresented in the fecal microbiota (Rebyota) studies.

According to the clinical experts, fecal microbiota (Rebyota) can be considered very similar to the product that is being administered through conventional FMT. However, while fecal microbiota (Rebyota) relies on a single administration, FMT programs may routinely offer repeated doses over 1 week. The clinical experts indicated that although FMT is effective at preventing rCDI, it is not readily available to many patients

in Canada. Issues surrounding limited access to FMT included the lack of public or private funding, the infrastructures and level of expertise required to run an FMT program, as well as challenges in establishing and maintaining stool banks for FMT. Fecal microbiota (Rebyota) would be regulated in terms of stability, reliability, and quality standards, and it is expected to take away the onus of managing stool banks from FMT providers. As such, having a commercial version of fecal microbiota (Rebyota) can potentially increase access to treatment in Canada, which was viewed by the clinical experts as an acceptable trade-off despite the single administration. In addition, the clinical experts indicated to the CDA-AMC clinical review team the possibility that conventional FMT programs may be shut down by Health Canada due to the availability of a commercial product. Health Canada notified CDA-AMC that clinicians were advised that, although fecal microbiota (Rebyota) has been authorized, it is not yet marketed. Therefore, no changes will be made to the current interim policy outlined in the guidance document *Fecal Microbiota Therapy Used in the Treatment of Clostridioides difficile Infection Not Responsive to Conventional Therapies*. Once fecal microbiota (Rebyota) becomes marketed, Health Canada will explore options for transitioning away from the interim policy, with further details to be provided in due course.

The experts indicated that fecal microbiota (Rebyota) may therefore cause a shift in the current treatment paradigm through increased availability, as long as the health care systems can provide the funding, infrastructures, and resources related to administration of the product.

The clinical experts suggested that prescribing and treatment administration of fecal microbiota (Rebyota) should be limited to clinicians and health care teams with expertise in the management of patients with rCDI and, ideally, in providing FMT, so to optimize the selection of patients who may benefit the most from treatment with fecal microbiota (Rebyota). In addition, the experts emphasized that both fecal microbiota (Rebyota) and conventional FMT are not risk-free and require a thorough informed consent process, as is the SOC for any intervention. The clinical experts highlighted the importance of follow-up after fecal microbiota (Rebyota) administration. Experience from clinical practice suggests that symptoms at 1 month are most predictive of long-term prognosis. The experts do not expect that all patients would go back to their pre-CDI baseline of bowel habits; however, the goal remains to reduce symptoms to a reasonable level and achieve a better quality of life while avoiding chronic antibiotic use.

### Clinician Group Input

One clinician group, the Canadian Antimicrobial Resistance Alliance, provided input for this review. The input stated that fecal microbiota (Rebyota) demonstrates efficacy and safety in patients with rCDI, offering a first in class live therapeutic option. The input noted that fecal microbiota (Rebyota) is an antimicrobial stewardship solution, as it reduces reliance on prolonged courses of vancomycin or fidaxomicin. The input stated that the treatment under review would be most appropriate for patients that have experienced at least 2 CDI recurrences, particularly for high-risk groups such as patients who are being hospitalized, older adults, patients with severe disease, or with immunocompromised conditions.

## Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for fecal microbiota (Rebyota):

- considerations for comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues.

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

### Table 2: Responses to Questions From the Drug Programs

| Implementation issues | Response |
|---|---|
| **Relevant comparators** | |
| The PUNCH CD2 and PUNCH CD3 trials were both placebo-controlled. There were no active comparators. The PUNCH OLS study was single arm.<br>Is placebo the most appropriate comparator?<br>The sponsor states that "antibiotics treat the infection thus are not considered comparators." Is this accurate? | The clinical experts noted to CDEC that placebo was appropriate in the context of a clinical trial, as long as patients were receiving an appropriate therapy for the number of recurrences, which could not be confirmed; however, as the PUNCH CD3 trial did not report the type of antibiotic regimen used (e.g., whether patients with more than 1 recurrence of CDI received a taper or pulse regimen). |
| Current guidelines indicate a second (or subsequent) recurrence should be treated with tapering vancomycin regimen.<br>Is this what is currently done in clinical practice? | The clinical experts noted to CDEC that this is what is being done in clinical practice. Shorter courses of antibiotics, even up to 21 days, would not be sufficient to manage multiply-recurrent disease according to the experts. |
| **Considerations for initiation of therapy** | |
| PUNCH CD2 trial: Phase IIb RCT. Enrolled 133 patients with **at least 2 recurrences** of CDI, or 2 episodes of CDI requiring hospitalization.<br>PUNCH CD3 trial: Phase III RCT. Enrolled 289 patients with **at least 1 recurrence** of CDI, or 2 episodes of CDI requiring hospitalization.<br>PUNCH OLS study: Phase III open-label study. Enrolled 698 patients with **at least 1 recurrence** of CDI, or 2 episodes of CDI requiring hospitalization.<br>Canadian, US, and European guidelines state that FMT may be considered at the second recurrence.<br>• Should the place in therapy for fecal microbiota (Rebyota) be aligned with the guidelines? Where do you expect to include | The clinical experts agree that the place in therapy for fecal microbiota (Rebyota) should be aligned with the guidelines, and that the treatment should be available to patients who have experienced at least 2 recurrences.<br>In addition, the clinical experts highlighted that a vancomycin taper or pulse regimen should be used before considering fecal microbiota (Rebyota), as it can resolve recurrences in many patients who experience multiple rCDIs. Also, the administration of stool-derived products such as fecal microbiota (Rebyota) and FMT carries some potential risks. Adequate patient selection is considered important.<br>The clinical experts did not consider the history of hospitalization as relevant to decision-making. The main treatment goal is to improve long-term quality of life, which applies to both inpatients |

| Implementation issues | Response |
|---|---|
| fecal microbiota (Rebyota) while treating recurrences?<br>• Should taper or pulse regimen be used before considering fecal microbiota (Rebyota)?<br>• Should treatment with fecal microbiota (Rebyota) be reserved for patients with a history of hospitalizations? | and outpatients. The clinical experts noted that patients can be safely managed outside of the hospital setting. |
| In the PUNCH CD2 and PUNCH CD3 trials, patients were stratified based on prior antibiotic use. Very few patients received fidaxomicin pretreatment. The best evidence supports fidaxomicin for the first recurrence of CDI. Sustained clinical cure after 30 days is approximately 70% with fidaxomicin vs. approximately 55% for vancomycin for rCDI.<br>Were participants potentially undertreated before placebo treatment, and does this inappropriately favour the fecal microbiota (Rebyota) product? | According to the clinical experts, although there is opportunity to do better with early use of fidaxomicin, this reflects the current reality in clinical practice. Fidaxomicin is an expensive drug that is currently not accessible to most patients for the treatment of a first episode or first recurrence of CDI.<br>However, as the PUNCH CD3 trial did not report the type of antibiotic regimen used (e.g., whether patients received a taper or pulse regimen), whether patients were receiving an appropriate therapy for the number of recurrences in the study could not be confirmed. |
| Treatment success rate is about 75% to 80%, meaning some patients will require an additional dose.<br>• How many days after initial treatment with fecal microbiota (Rebyota) must pass before it should be decided if a second dose is required?<br>• What is the evidence for a third dose of fecal microbiota (Rebyota), should the first 2 be deemed to fail?<br>• What is the window outside which the CDI episode is considered a new infection and starts the full treatment paradigm again?<br>• Would fecal microbiota (Rebyota) be used earlier on during therapy in patients experiencing a new infection episode? Does that first infection need to have included fecal microbiota (Rebyota) in the treatment protocol? | The clinical experts indicated that some conventional FMT programs routinely provide several administrations of FMT per patient as a treatment plan. This is based on prior experience with FMT, where there is evidence of increased effectiveness with the number of doses. The clinical experts showed concerns regarding the potential lower magnitude of effect with administration of only 1 dose of fecal microbiota (Rebyota) as the total regimen for preventing an rCDI. Indeed, as per the Health Canada indication, a second dose of fecal microbiota (Rebyota) is only recommended in case of a recurrence; however, the clinical experts indicated that in the context of an FMT program, they would not consider administering a second round of single-dose FMT through the same mode of administration following a recurrence.<br>Most rCDI would typically be expected to occur within 4 to 8 weeks. If a recurrence occurs, patients then need to receive a new antibiotic course of vancomycin though a taper or pulse regimen to get immediate symptom relief and reduce active inflammation before considering any additional administration of fecal microbiota (Rebyota) or FMT.<br>The window outside which the CDI episode is considered a new infection would be a matter of clinical judgment. The experts mentioned that an unprovoked recurrence of CDI after 6 to 12 months may be considered a new episode. The treatment sequence would remain the same.<br>CDEC recommended that reimbursement for fecal microbiota (Rebyota) should be limited to a single initial dose. In the case of a CDI recurrence after the first dose, an additional single dose may be eligible for reimbursement per recurrence, provided that the original initiation criteria remain applicable. |
| **Considerations for discontinuation of therapy** | |
| When is subsequent treatment with fecal microbiota (Rebyota) considered futile, i.e., following the second dose or the third? | The clinical experts noted that some conventional FMT programs use a full series of FMT treatments given throughout 1 week and observe. If a recurrence occurs, the experts would |

| Implementation issues | Response |
|---|---|
| | consider repeating FMT either with a more aggressive treatment approach or by using a different route of administration (e.g., capsules or colonoscopy), after a course of vancomycin though a taper or pulse regimen.<br>However, this would not apply to fecal microbiota (Rebyota), as the recommended dosage differs by being a single-dose enema. As previously mentioned, the clinical experts would not consider administering a second round of single-dose FMT through the same mode of administration following a recurrence.<br>The clinical experts felt that limiting to 1 dose may lead to less successful outcomes than a series of doses upfront, as there are growing data with FMT suggesting that the additional doses improve the overall success rate.<br>CDEC recommended that reimbursement for fecal microbiota (Rebyota) should be limited to a single initial dose. In the case of a CDI recurrence after the first dose, an additional single dose may be eligible for reimbursement per recurrence, provided that the original initiation criteria remain applicable. |
| **Considerations for prescribing of therapy** | |
| Should fecal microbiota (Rebyota) only be prescribed by an infectious diseases' specialist or gastroenterologist? | The clinical experts agreed that prescribing and treatment administration of fecal microbiota (Rebyota) should be limited to clinicians and health care teams with expertise in the management of patients with rCDI and, ideally, in providing FMT.<br>This will allow optimization of the selection of patients who may benefit the most from treatment with fecal microbiota (Rebyota), hopefully limiting the overdiagnosis of rCDI in patients who are colonized with *Clostridioides difficile* and have other etiologies for diarrhea.<br>In addition, the experts emphasized that both fecal microbiota (Rebyota) and FMT are not risk-free and that providers should be aware of the risks and alternatives in discussing treatment options with patients. |
| This product is administered rectally by a nurse or clinician which requires clinician time and expertise. There is no anesthesia or colonoscopy required. Do you foresee that this will cause challenges for patients living in rural areas? | The clinical experts noted that limiting to clinicians and health care teams with expertise in the management of patients with rCDI and in providing FMT may cause challenges for patients living in rural areas at first; however, capacity can be built, and the procedure is relatively simple. |
| Fecal microbiota (Rebyota) needs to be kept frozen in an ultracold freezer at −60°C to −90°C (until its expiration) or in a regular refrigerator for up to 5 days (including the 24-hour thawing period). It must be thawed in the refrigerator for 24 hours before use. Keeping in mind that availability of ultracold freezers is limited within the hospital and/or health authority structure and almost nonexistent in community pharmacies making distribution challenging, how does the sponsor intend to distribute this product? | The sponsor noted that a PSP will be offered to support specialty pharmacy dispensing, among other services. In association with the PSP, fecal microbiota (Rebyota) will be warehoused and openly distributed by a third-party logistics provider located in Canada. Fecal microbiota (Rebyota) will be stored in an ultracold freezer until a pharmacy places an order. Fecal microbiota (Rebyota) and ancillary supplies (i.e., administration kit) will be shipped directly to the dispensing pharmacy with validated cold chain packaging based on the pharmacy's product management capabilities for just in time delivery to the administration site (e.g., hospital or clinic). The validated pack out container can maintain the ultracold temperature for 72 hours. The product |

| Implementation issues | Response |
|---|---|
| | is also stable at 2°C to 8°C (36°F to 46°F) for up to 5 days (including the 24-hour thawing period). |
| **Generalizability** | |
| The guidelines discuss the potential role for FMT in refractory CDI. This is a rare situation with limited published evidence. Does the evidence show there is a place for this product in refractory CDI? What is the real-world experience with FMT in patients who are refractory? | The clinical experts noted that genuine refractory CDI is rare. In their experience, what is thought to be a refractory CDI may usually be another condition that was misdiagnosed. The evidence regarding the effect of FMT in patients with refractory CDI is limited, and unknown with fecal microbiota (Rebyota). |
| **Care provision issues** | |
| How soon after administration would diarrhea be considered to have rendered the treatment insufficient? | The clinical experts indicated that this is an area of uncertainty. One clinical expert mentioned that in their FMT program, the product should be retained in the bowel for a minimum of 20 minutes. However, there is no evidence to inform on the correlation between longer retention and improved outcomes.<br>Minor diarrhea and changes in stool patterns are common immediately after FMT and should be monitored for progression in the following days (beyond 48 to 72 hours).<br>Recurrences can occur very soon after FMT (first few days) or weeks afterwards. It depends on the individual's pattern of disease and risk factors for recurrence. |

CDEC = Canadian Drug Expert Committee; CDI = *Clostridioides difficile* infection; FMT = fecal microbiota transplant; PSP = patient support program; rCDI = recurrent *Clostridioides difficile* infection; RCT = randomized controlled trial; vs. = versus.

# Clinical Evidence

## Systematic Review

### Description of Studies

One study was reviewed. PUNCH CD3 (n = 289) was a phase III, multicentre, double-blind, placebo-controlled RCT designed to evaluate the efficacy and safety of fecal microbiota (Rebyota) to prevent recurrence of CDI in adult patients following antibiotic treatment for rCDI. Patients could enter the trial if they had at least 1 recurrence after a primary episode, with at least 1 round of oral antibiotic therapy. Fecal microbiota (Rebyota) was administered as 1 single-dose enema.

The primary outcome was the recurrence of CDI over 8 weeks, which was defined as the presence of CDI diarrhea, with a positive stool test for the presence of *Clostridioides difficile* toxin, within 8 weeks of administration of a study enema. The primary efficacy analysis was performed using a Bayesian hierarchical model, which formally incorporated data about the treatment effect of fecal microbiota (Rebyota) from the prior randomized placebo-controlled phase IIb PUNCH CD2 trial. To account for potential heterogeneity between the populations across the 2 trials, a dynamic borrowing approach was used. This method allowed for more data to be borrowed from the previous trial when the response rates were similar.

In patients who had previously achieved treatment success at 8 weeks, sustained clinical response at 6 months was assessed as the secondary end point in the study. HRQoL was an exploratory outcome in the studies and was assessed using the Cdiff32, a validated, disease-specific assessment tool indicating how a person is affected by CDI-related physical, mental, and social health concerns. The total and domain scores of Cdiff32 range from 0 to 100, where lower scores denote a greater negative impact on quality of life. An MCID of 10 points has been suggested in the literature based on a distribution-based approach.

## Efficacy Results

### *Response to Treatment at 8 Weeks*

For the primary outcome, the mean success rate was 70.4% in the fecal microbiota (Rebyota) group and 58.1% in the placebo group. The between-group difference in mean success rate was 12.3% (95% CrI, 1.4% to 23.3%) based on posterior estimates from the Bayesian hierarchical model.

The between-group difference for treatment success was [redacted] in patients who had no more than 3 prior CDI episodes (or 2 CDI recurrences) and [redacted] in patients who had more than 3 prior CDI episodes (or more than 2 CDI recurrences). In patients who received vancomycin alone, the between-group difference was [redacted] in patients who were treated for no more than 14 days and [redacted] in patients who were treated for more than 14 days.

Treatment with fecal microbiota (Rebyota) may not result in a clinically important increase in the proportions of patients with sustained clinical response at 6 months, among patients who previously achieved treatment success at 8 weeks, compared to placebo, based on a between-group difference of 1.5% [redacted]).

### *Health-Related Quality of Life*

HRQoL was assessed as an exploratory outcome. HRQoL was not tested statistically, and the results are considered as supportive evidence. Results suggest that treatment with fecal microbiota (Rebyota) may result in little to no difference in the change from baseline in HRQoL as measured with the Cdiff32 over 8 weeks compared to placebo. The mean between-group difference in change from baseline through 8 weeks in Cdiff32 was 5.71 ([redacted]).

The sponsor provided an additional exploratory analysis of HRQoL data in patients who responded at 8 weeks. In both the main study population and the patients who responded, the between-group differences reported in overall Cdiff32 scores crossed the null and were modest, especially relative to the large within-group improvements seen in both patients who were receiving fecal microbiota (Rebyota) and those receiving placebo. Although statistical significance was achieved for the mental domain summary in patients who responded, these domain-level results are from exploratory analyses without multiplicity adjustment and from restricted subsets of patients who responded, increasing the risk of chance findings. In addition, limited details were provided for proper appraisal, including for formal assessment of the magnitude of effect and clinical relevance of the findings.

### *Stool Testing – Fecal Microbial Composition*

Fecal sequencing analysis suggests that the microbiome composition of patients experiencing treatment success changed from baseline over all time points ($P < 0.001$ for within-group change from baseline using the generalized Wald test). The change in microbiome composition after treatment was characterized by an increase in *Bacteroidia*-class and *Clostridia*-class bacteria, together with a decrease in *Gammaproteobacteria* and *Bacilli*-class bacteria.

### *Health Care Resource Utilization*

Hospitalizations and intensive care unit admissions were reported as harms outcomes for patients who were [redacted]. A total of 2 patients in the fecal microbiota (Rebyota) group required intensive care unit admissions within the 8-week follow-up of blinded treatment. No patient experienced major complications of CDI after receiving an open-label fecal microbiota (Rebyota) enema in this treatment group.

## Harms Results

A relatively high proportion of patients receiving fecal microbiota (Rebyota) in the PUNCH CD3 trial [redacted] experienced at least 1 adverse event (AE), compared with [redacted] in the placebo group. These were numerically more frequent in patients who received 2 fecal microbiota (Rebyota) enemas [redacted] compared to patients who received only 1 fecal microbiota (Rebyota) enema [redacted]. The most common treatment-emergent AEs (TEAEs) were related to gastrointestinal disorders and included diarrhea, abdominal pain, nausea, and abdominal distention.

Serious AEs (SAEs) were relatively uncommon in patients receiving fecal microbiota (Rebyota) enema ([redacted] or placebo [redacted] but were also numerically more frequent in patients who received 2 fecal microbiota (Rebyota) enemas [redacted] than in patients who received only 1 fecal microbiota (Rebyota) enema [redacted]. Two deaths were reported throughout the trial's duration in patients who received fecal microbiota (Rebyota) which were not related to the study drug or enema procedure according to the sponsor. The sponsor reported no events of toxic megacolon or colonic perforation; however, 1 patient in the fecal microbiota (Rebyota) group experienced septic shock and emergency colectomy as major complications of new CDI.

Overall, the clinical experts indicated that the harms profile of fecal microbiota (Rebyota) did not raise any new safety signal. However, as with most clinical trials, the study was not powered to detect infrequent AEs or designed to detect those with a lag time. The clinical experts indicated that there may be long-term, unintended effects of manipulating a patient's microbiome, such as affecting the risk of developing a range of conditions over time, the impact of which is currently unknown.

## Critical Appraisal

Although the randomization methods were appropriate for reducing the risk of bias in the randomization process, more patients in the fecal microbiota (Rebyota) group than the placebo group had 2 or more prior CDI recurrences, introducing a possible risk of bias of uncertain direction or magnitude, although it may have directionally favoured placebo.

As patients who experienced treatment failure at 8 weeks could receive open-label fecal microbiota (Rebyota), interpretation of end points tested beyond 8 weeks is challenged by the fact that a proportion of patients in the placebo group had received fecal microbiota (Rebyota).

There is uncertainty surrounding interpretation of the findings. Since no MCID was reported in the literature as a threshold for treatment success, the presence of an important effect was informed by the clinical experts consulted for this review. The point estimate (12.3%) suggests the presence of a clinically important effect; however, the lower bound of the 95% CrI (1.4%) is consistent with a trivial effect that would not be considered clinically important for patients. For HRQoL, the magnitude of the findings from the Cdiff32 was not considered clinically meaningful by the clinical experts consulted for this review. An MCID of 10 points was estimated in the literature using a distribution-based approach, so it may not fully reflect a change that is important for patients. Further, the MCID was suggested for within-group changes, rather than for between-group differences. In addition, there is a risk of bias due to missing outcome data at 6 months, as relatively few patients in both groups were available for HRQoL assessments, and missing data were imputed using the last observation carried forward (LOCF), which relies on assumptions about the trajectory of the end point that may not be plausible.

Sustained clinical response at 6 months was measured among patients with a response at 8 weeks; therefore, there is a risk of bias in the measurement of this end point as it is uncertain that prognostic balance would be maintained in this subpopulation.

Input from clinical experts suggested that findings from the PUNCH CD3 trial may be considered generalizable to patients considered overall at a lower risk of experiencing CDI recurrences than patients typically seen in clinical practice, who would be the best candidates to receive fecal microbiota (Rebyota). This was based on the low number of previous CDI recurrences in the trial, as well as on the exclusion of patients with relevant comorbidities. In addition, it is uncertain whether patients previously received an appropriate antibiotic regimen for the treatment of the qualifying CDI episode. The trial could not inform on the comparative effectiveness and safety of fecal microbiota (Rebyota) relative to other currently used therapies for rCDI, such as conventional FMT.

## GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from the PUNCH CD3 trial started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- treatment success rate
- sustained clinical response among patients who previously achieved treatment success
- HRQoL (Cdiff32)
- SAEs.

## Table 3: Summary of Findings for Fecal Microbiota (Rebyota) vs. Placebo for Patients With rCDI

| Outcome and follow-up | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Placebo | Fecal microbiota (Rebyota) | Difference | | |
| **Clinical response** | | | | | | | |
| Treatment success rate<br>Follow-up: 8 weeks | 262<br>(1 RCT) | NR | Mean:<br>58.1% | Mean (95% CrI):<br>70.4% [redacted] | Mean (95% CrI):<br>12.3%<br>(1.4% to 23.3%) | Moderate[a] | Fecal microbiota (Rebyota) likely results in a clinically important increase in treatment success rate over 8 weeks compared to placebo. |
| Proportion of patients with sustained clinical response among patients who previously achieved treatment success | 179<br>(1 RCT) | NR | [redacted] | [redacted] | [redacted] | Low[b] | Fecal microbiota (Rebyota) may result in little to no clinically important difference in the proportions of patients with sustained clinical response, among patients who previously |

| Outcome and follow-up | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Placebo | Fecal microbiota (Rebyota) | Difference | | |
| Follow-up: 6 months | | | | | | | achieved treatment success, over 6 months compared to placebo. |
| **HRQoL** | | | | | | | |
| Mean change from baseline in Cdiff32 scores (0 [worst] to 100 [best])<br>Follow-up: 8 weeks | 262 (1 RCT) | NA | [redacted] | [redacted] | 5.71 [redacted] | Moderate[c] | Fecal microbiota (Rebyota) may result in little to no clinically important difference in HRQoL as measured with the Cdiff32 over 8 weeks compared to placebo. |
| Mean change from baseline in Cdiff32 scores (0 [worst] to 100 [best])<br>Follow-up: 6 months | 262 (1 RCT) | NA | [redacted] | [redacted] | [redacted] | Very low[d] | The evidence is very uncertain about the effect of fecal microbiota (Rebyota) on HRQoL at 6 months compared with placebo. |
| **Harms** | | | | | | | |
| Patients with ≥ 1 SAE<br>Follow-up: 6 months | 267 (1 RCT) | NR | [redacted] | [redacted] (NR) | [redacted] (NR) | Low[e] | Fecal microbiota (Rebyota) may result in little to no clinically important difference in the proportion of patients with ≥ 1 SAEs over 6 months compared to placebo. |

Cdiff32 = *Clostridioides difficile* Quality of Life Survey; CI = confidence interval; CrI = credible interval; HRQoL = health-related quality of life; LOCF = last observation carried forward; MCID = minimum clinically important difference; NA = not applicable; NR = not reported; rCDI = recurrent *Clostridioides difficile* infection; RCT = randomized controlled trial; SAE = serious adverse event; vs. = versus.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]Treatment success: Rated down 1 level for imprecision. The presence of an important effect was informed by the clinical expert consulted for this review. The point estimate (12.3%) suggests the presence of a clinically important effect; however, the lower bound of the 95% CrI (1.4%) is consistent with an effect that would not be considered clinically important for patients.

[b]Sustained clinical response: Rated down as follows: 1 level for imprecision (The presence of an important effect was informed by the clinical expert consulted for this review. The point estimate (1.5%) suggests a trivial effect that would not be considered clinically important for patients; however, the lower bound [redacted] and

upper bound ( [redacted] of the CrI could be consistent with either a clinically important decrease or increase, respectively, in sustained clinical response); and 1 level for study limitation (There likely was a loss of prognosis balance in the subpopulation of patients analyzed, as it consisted of patients who previously achieved treatment success at 8 weeks).

[c]HRQoL: Rated down 1 level for imprecision. The Cdiff32 was assessed as an exploratory outcome. Change from baseline in Cdiff32 score was not tested statistically in the trial and should be considered as supportive evidence. Although the point estimate for the between-group difference suggests little to no clinically important difference based on a suggested MCID of 10 points, the upper bound of the 95% CI suggests the possibility of a clinically important difference between fecal microbiota (Rebyota) and placebo. The MCID of 10 points suggested in the literature for this instrument is however uncertain, as it was estimated using a distribution-based approach. As distribution-based methods rely on statistical properties of the data, they may not always reflect clinically meaningful changes for patients' perspectives. This MCID was also estimated for within-group changes, rather than between-group differences.

[d]HRQoL. Rated down as follows: 1 level for serious imprecision (Although the point estimate for the between-group difference suggests little to no clinically important difference based on a suggested MCID of 10 points, the lower bound of the 95% CI suggests clinically important detriment with fecal microbiota [Rebyota] compared to placebo. The MCID of 10 points suggested in the literature for this instrument is uncertain, as it was estimated using a distribution-based approach. As distribution-based methods rely on statistical properties of the data, they may not always reflect clinically meaningful changes for patients' perspectives. This MCID was also estimated for within-group changes, rather than between-group differences); and 2 levels for very serious study limitations (Few patients completed the 6-month assessments. LOCF was used to impute missing outcome data, an approach that relies on assumptions about the missing data that are unlikely to be realistic. Further, some patients in the placebo group had received open-label fecal microbiota [Rebyota]. The Cdiff32 was assessed as an exploratory outcome. Statistical testing for the Cdiff32 was not adjusted for multiplicity in the trial and should be considered as supportive evidence).

[e]Harms: Rated down 1 level for imprecision, as the between-group effect estimate was based on few events, and 1 level for study limitation, as some patients in the placebo group received active treatment with open-label fecal microbiota (Rebyota).

Source: Clinical Trial Report PUNCH CD3. Details included in the table are from the sponsor's Summary of Clinical Evidence.

## Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor for this review.

## Indirect Comparisons

No ITCs were submitted by the sponsor for this review. According to the sponsor, there are no comparators to fecal microbiota (Rebyota) in Canada for the preventive treatment of rCDI after antibiotic treatment for rCDI. In clinical practice, treatment options include long-term vancomycin administered in a taper or pulse regimen, and conventional FMT.

## Studies Addressing Gaps in the Evidence From the Systematic Review

### PUNCH CD2 Trial

#### *Description of Study*

PUNCH CD2 (N = 133) was a phase II, prospective, multicentre, double-blind, randomized, placebo-controlled trial designed to assess the efficacy and safety of fecal microbiota (Rebyota) for rCDI and to establish a treatment regimen for subsequent confirmation in the PUNCH CD3 trial. The study included adults (aged ≥ 18 years) with rCDI, requiring at least 2 CDI recurrences and at least 2 rounds of SOC oral antibiotic therapy or 2 severe CDI episodes resulting in hospitalization. A total of 150 patients were enrolled, 133 of which were randomized into 3 groups: group A (N = 45), group B (N = 44), and group C (N = 44). Patients were randomized 1:1:1 to receive either 2 fecal microbiota (Rebyota) enemas (group A), 2 doses of placebo (group B), or 1 dose of fecal microbiota (Rebyota) followed by 1 dose of placebo (group C). Doses were administered 7 days apart. If patients experienced CDI recurrence within 8 weeks posttreatment, they could choose either SOC treatment or a second open-label fecal microbiota (Rebyota) course. This report primarily focuses on groups B and C, aligning with Health Canada's proposed recommended 1-dose fecal microbiota (Rebyota) regimen.

### *Efficacy and Harms Results*

Efficacy results in the intention-to-treat (ITT) population showed that at 8 weeks after treatment completion, treatment success rates were 43.2% (19 of 44) for group B and 56.8% (25 of 44) for group C, with a difference of 13.6% (95% CI, [redacted] P = 0.201). The 25th percentile time to recurrence, estimated by the Kaplan-Meier method was 8.0 days in both group B (95% CI, | [redacted]) and group C (95% CI, | [redacted]). The combined treatment success rate (defined as no *Clostridioides difficile* associated disease and no need for re-treatment or fecal transplant by day 56 after the last study enema) of all patients in the open-label portion was [redacted]). Additionally, HRQoL was assessed using the Short Form (36) Health Survey (SF-36). Baseline values were comparable between groups and both treatment groups showed a numerical increase in mean scores for all SF-36 components from baseline to week 8. Between-group differences were not reported. Safety was assessed up to 24 months posttreatment. TEAEs occurred in 86.4% of group B and 78.6% of group C. TEAEs including anemia, nausea, flatulence, hematochezia, pyrexia, pneumonia, falls, and dyspnea were more frequent in group C than group B. SAEs were reported in 36.4% and 35.7% of patients in group B and C, respectively, none of which were considered treatment related according to the sponsor. Deaths occurred in [redacted] (group B) and [redacted] (group C) of patients, primarily due to pre-existing conditions.

### *Critical Appraisal*

The PUNCH CD2 trial provided additional data on CDI recurrence, HRQoL (SF-36), and long-term safety up to 24 months. The primary efficacy analysis (ITT) did not reject the null hypothesis, and secondary comparisons proceeded without alpha adjustment, increasing the risk of false positives in the secondary analysis results. Due to the small sample sizes across groups, there is an increased risk that prognostic balance was not achieved (as evidenced by imbalances across groups by sex and prior hospitalization for CDI). As such, it is possible that the observed effects were either overestimated or underestimated. The study is limited by the lack of placebo control beyond 8 weeks of treatment; as such, results beyond 8 weeks are confounded by open-label fecal microbiota (Rebyota) use in the placebo group. In the analysis of the SF-36 there is a risk of bias due to missing outcome data. Data were missing for up to 30% of patients across groups at 8 weeks. These data were imputed using the LOCF, a single-imputation method that relies on the assumption that HRQoL remained constant over time since the last available assessment, which is unlikely reasonable. Patients who were immunocompromised were excluded, raising concerns about pathogen transmission. Most patients (89.5%) used vancomycin, aligning with clinical practice, as fidaxomicin is rarely used for rCDI in Canada.

## PUNCH OLS Study

### *Description of Study*

PUNCH OLS (N = 698) was a phase III, prospective, multicentre, open-label, single-arm study. The objective of the study was to evaluate the safety, tolerability, and effectiveness of fecal microbiota (Rebyota) for single and repeat administration in a broader population of patients with conditions which were excluded from previous trials, such as Crohn disease, ulcerative colitis, IBD, IBS, and immunocompromised conditions.

### *Efficacy Results*

Of 676 patients in the primary efficacy analysis, 499 patients (73.8%) reported to have treatment success within 8 weeks of the first dose of fecal microbiota (Rebyota) which was defined as the absence of CDI diarrhea through 8 weeks after completing the first dose. Similar treatment success rates were observed across most demographic subgroups including sex, race, ethnic group, site geography, number of prior CDI episodes, and Cdiff32 score; however, the treatment effect appeared of smaller magnitude in patients aged 65 years and older.

A total of 151 patients experienced a recurrence of CDI after the first dose, and of these, 121 patients received a second dose of fecal microbiota (Rebyota). Treatment success was then achieved in 67 patients (55.4%).

Among patients who completed the 6-month follow-up, the sustained clinical response rate of fecal microbiota (Rebyota) among patients who previously achieved treatment success was 91.0%.

The mean (standard deviation) change from screening to 6 months in the Cdiff32 scores was [redacted].

### *Harms Results*

Of the 697 patients included in the safety population, [redacted] patients reported AEs following fecal microbiota (Rebyota) administration. These were mostly mild (20.4%) to moderate [redacted] in severity and the most frequently reported included gastrointestinal disorders and infections.

### *Critical Appraisal*

The single-arm nature of the PUNCH OLS study does not allow for causal conclusions to be drawn regarding the efficacy and safety of fecal microbiota (Rebyota). Knowledge of treatment received is subject to introducing bias in the assessment of subjective outcomes. Although the selection criteria allowed for a broader population, the number of patients enrolled in the study with Crohn disease, ulcerative colitis, IBD, IBS, and immunocompromised conditions was small. Therefore, the generalizability of the findings to patients who have these coexisting comorbidities remains uncertain.

## Study by Feuerstadt et al.

Feuerstadt et al., a retrospective study (N = 94), assessed the effectiveness and safety of fecal microbiota (Rebyota) in adults with rCDI using broad eligibility criteria to reflect real-world conditions, including those with comorbidities such as IBS, IBD, or immunocompromising conditions. The study enrolled patients across 5 study sites in the US from 2015 to 2019. Patients could receive up to 4 fecal microbiota (Rebyota) enemas (2 treatment courses of 2 doses each), per physician discretion. No lab confirmation of CDI was required, there were no exclusion criteria, and data were retrospectively collected via chart review. The mean age was 59.8 years, 44.7% were 65 years or older, and 72.3% were female.

Sixty-six of the 94 patients (70.2%) in the full analysis set experienced treatment success (defined as no CDI recurrence within 8 weeks after the final treatment dose for the qualifying event) at week 8, of which 58 patients (87.9%) maintained a sustained clinical response through 6 months following treatment. TEAEs

occurred in 40 of 64 patients (62.5%) in the primary safety set, 17.2% of which were deemed product-related, and 4.7% were deemed procedure related by the investigators. Common TEAEs in the primary safety set included abdominal pain (14.1%), diarrhea (14.1%), and urinary tract infection (10.9%). SAEs occurred in 12.5%, with 1 death (1.6%) due to multiorgan failure, unrelated to treatment according to the investigators.

The study included broad eligibility criteria but the noncomparative nature of its design does not allow for causal conclusions to be drawn regarding the efficacy and harms of fecal microbiota (Rebyota). Subjective outcome reporting may be biased, and dosing could have exceeded Health Canada's 1-dose recommendation.

### Study by Lee et al.

The summary included pooled safety data from 5 prospective studies, incorporating 3 phase II studies (PUNCH CD, PUNCH CD2, and PUNCH Open-Label) and 2 phase III studies (PUNCH CD3 and PUNCH OLS). These studies evaluated the cumulative safety of fecal microbiota (Rebyota) using standardized manufacturing practices and evolving pathogen screening to ensure safety.

All trials enrolled adults aged at least 18 years with rCDI who had received antibiotics for their CDI episode before study treatment. Dosing regimens varied, with patients receiving either a single dose or 2 doses of fecal microbiota (Rebyota) and/or placebo, administered 7 plus or minus 2 days apart. Four trials allowed open-label treatment if CDI recurrence was confirmed within 8 weeks of the initial course. The full population included 978 patients who received at least 1 dose of fecal microbiota (Rebyota) and 83 patients who received placebo. At baseline, the pooled trial data showed that a higher proportion of patients in the fecal microbiota (Rebyota) group were aged 65 years or older compared to the placebo group (48.2% versus 37.3%). Additionally, more patients in the fecal microbiota (Rebyota) group (78.0%), placebo plus fecal microbiota (Rebyota) group (83.3%), and fecal microbiota (Rebyota) plus open-label fecal microbiota (Rebyota) group (79.6%) had 3 or more CDI episodes before trial entry than those in the placebo group (68.7%).

The primary outcome measured the number of patients experiencing fecal microbiota (Rebyota) and/or procedure-related TEAEs, defined as AEs occurring on or after the day of treatment. Most common TEAEs were gastrointestinal disorders, mostly mild or moderate in severity. Serious TEAEs were similar between placebo (60.2%) and fecal microbiota (Rebyota) 1-dose (66.4%) groups, but higher in blinded or any fecal microbiota (Rebyota) groups (68.8%). Eighteen deaths were reported, all in patients who received fecal microbiota (Rebyota) although none were considered related to the treatment.

Limitations include heterogeneity in study protocols, varied dosing regimens, and differences in patient populations, affecting internal validity. Open-label treatments could introduce bias in reporting subjective AEs. Pooling data from multiple trials may obscure specific interactions or effects, impacting safety outcome interpretations.

Study by Khanna et al.

The sponsor provided additional data from a retrospective cohort study by Khanna et al. (2025). In this study of 196 adults in the US with rCDI who received fecal microbiota (Rebyota) between July 2023 and August 2024, the overall treatment success rate at 8 weeks was 83%. In the overall population, most patients (n = 136) had at least 3 prior CDI recurrences. Success rates were consistent across the number of prior recurrences subgroups. However, the study had important limitations. Baseline patient characteristics were limited, with no detailed information on the exact number of prior CDI episodes, comorbidities, or antibiotic regimen used other than product name, preventing assessment of their impact on outcomes. The analyses did not adjust for confounding factors, lacked a control arm, and may be subject to selection bias due to its nonrandomized design. Differences in health care access and the predominance of treatment in infusion centres in the southern and western US may further limit the generalizability of the findings. As such, the results should be considered as supportive evidence.

## Ethical Considerations

Patient group, clinician group, and drug plan input, as well as consultation with clinical experts were reviewed to identify ethical considerations associated with the use of fecal microbiota (Rebyota) to prevent recurrence of CDI in adults following antibiotic treatment for rCDI.

- **Diagnosis, treatment, and experiences of rCDI:** rCDI is a highly burdensome condition that can significantly diminish quality of life, disrupt daily functioning, and cause prolonged psychological distress for both patients and caregivers. Each recurrence increases the risk of future episodes, trapping individuals in a cycle of worsening illness and fear of relapse. Those most affected by rCDI – including older adults, individuals who are immunocompromised, and people experiencing systemic barriers to care – often face compounding medical and structural vulnerabilities. While fecal microbiota-based therapies have demonstrated effectiveness in preventing recurrence, access to conventional FMT in Canada has been limited due to regulatory, logistical, and funding constraints, leaving many patients without timely and equitable access to a therapeutic option that has the potential to restore gut stability and reduce long-term hardship.
- **Clinical and economic evidence used in the evaluation of fecal microbiota (Rebyota):** Moderate certainty findings from the pivotal PUNCH CD3 trial suggest that treatment with fecal microbiota (Rebyota) likely results in a clinically important increase in treatment success rate over 8 weeks compared to placebo, but the design raises important evidentiary and ethical concerns. The absence of an active comparator (particularly conventional FMT) limits the trial's ability to assess relative effectiveness, while the inclusion of patients at lower risk, exclusion of populations likely to receive fecal microbiota (Rebyota) in practice, and lack of clarity around prior antibiotic regimens limit the generalizability of the study findings to routine clinical practice. These limitations create uncertainty about the benefits and risks of treatment for those most affected by rCDI, complicating informed consent, clinical decision-making, and health system decision-making.

- **Clinical use and implementation of fecal microbiota (Rebyota):** While fecal microbiota (Rebyota) may improve access to microbiota-based therapies, its potential implementation also raises important ethical considerations related to patient safety, informed consent, and appropriate prescribing. The absence of long-term safety data on both conventional FMT and fecal microbiota (Rebyota) creates challenges in fully informing patients of potential risks. There is also a risk of misdiagnosis of rCDI and subsequent inappropriate prescribing. While prescribing could be limited to specialists with expertise in rCDI and experience with fecal microbiota-based therapies, this could raise concerns regarding equitable access across geographic settings. In addition, as a standardized, single-dose enema, fecal microbiota (Rebyota) may not be suitable for all patients and may limit provider flexibility in selecting appropriate delivery modalities or tailoring dosing regimens to individual needs.
- **Health systems:** Fecal microbiota (Rebyota) may introduce both opportunities and challenges for health system integration. While it may help to alleviate some of the logistical burdens associated with donor screening and stool preparation, persistent geographic and health infrastructural barriers may continue to limit access, particularly for rural and remote populations. Current reliance on a single US-based manufacturer introduces the risk that supply disruptions could interrupt access to an otherwise effective therapy, raising ethical concerns about treatment continuity and equitable care.

# Economic Evidence

## Cost and Cost-Effectiveness

### Table 4: Summary of Economic Evidence

| Component | Description |
|---|---|
| **Type of economic evaluation** | Cost-utility analysis<br>Markov model |
| **Target population** | Adult patients with at least 1 rCDI resolved following antibiotic treatment |
| **Treatment** | Fecal microbiota (Rebyota) after prior antibiotic treatment (i.e., vancomycin, fidaxomicin) |
| **Dose regimen** | Single 150 mL dose via rectal administration |
| **Submitted price** | $9,125.00 per 150 mL liquid suspension |
| **Submitted treatment cost** | $9,125.00 per treatment course |
| **Comparator** | No preventive therapy after prior antibiotic treatment (i.e., vancomycin, fidaxomicin) |
| **Perspective** | Publicly funded health care payer<br>Societal (including patient productivity loss and travel costs) |
| **Outcomes** | QALYs, LYs |
| **Time horizon** | 5 years |
| **Key data sources** | PUNCH CD3 trial and PUNCH Open-Label Study |

| Component | Description |
|---|---|
| **Key limitations** | • The comparative efficacy of fecal microbiota (Rebyota) is uncertain. The sponsor assumed that the placebo arm of the PUNCH CD3 trial was representative of current standard of care, which is uncertain because it is unknown whether patients in both groups received an appropriate antibiotic regimen of vancomycin taper pulse for the treatment of the qualifying CDI episode. Further, the sponsor assumed the antibiotic treatment of patients before receiving fecal microbiota (Rebyota) and no preventive therapy would be different, which conflicts with the efficacy results from the PUNCH CD3 trial as patients were given a similar distribution of antibiotics in the fecal microbiota (Rebyota) and placebo arms. As well, there is no direct or indirect evidence submitted to evaluate fecal microbiota (Rebyota) relative to other currently used therapies for the prevention of rCDI, including FMT. Thus, no conclusion can be drawn on the comparative efficacy, safety, and cost-effectiveness of fecal microbiota (Rebyota) vs. other currently used therapies.<br>• The long-term clinical efficacy of fecal microbiota (Rebyota) is uncertain as efficacy beyond 6 months was based on a post hoc survival analysis of the PUNCH CD2 trial, which was a different clinical study, with a different patient population, than the source used to populate the primary efficacy parameters in the sponsor's model (i.e., treatment success at 8-weeks from the PUNCH CD3 trial). According to the CDA-AMC Clinical Review, no conclusions can be made regarding comparative sustained response beyond 6 months. Further, conclusions regarding sustained response at 6 months, among patients who achieved previous treatment success at 8 weeks, were that there was no clinically important difference between fecal microbiota (Rebyota) and placebo, and there may be no added benefit for fecal microbiota (Rebyota) in terms of sustained response.<br>• The sponsor assumed that patients in the model have homogenous experience with rCDI, meaning that patients will experience similar utilities and require similar health care resources in the rCDI health state. According to clinical expert feedback received for this review, this assumption is not reflective of the patient experience with rCDI as some patients will have symptom control with vancomycin suppression while others may experience acute, severe symptoms associated with rCDI. The heterogeneity in the rCDI health state has implications on costs and quality of life associated with the health state, as outlined in subsequent limitations.<br>• Due to limitations in the sponsor's model structure stemming from heterogeneity in the rCDI health state:<br>  ◦ The utility value assigned to the rCDI health state is likely not reflective of all patients in that state. As well, assumptions regarding return to baseline utility value upon resolution of rCDI was deemed to not meet face validity, based on clinical expert feedback received for this review. If the utility value assigned to the rCDI health state in the sponsor's model is underestimated, the sponsor's approach would favour fecal microbiota (Rebyota).<br>  ◦ The health care resource costs assigned to the rCDI health state are likely not reflective of all patients in that state. If the health state costs for rCDI in the sponsor's model are overestimated, the sponsor's approach would favour fecal microbiota (Rebyota).<br>• The impact of fecal microbiota (Rebyota) on mortality and colectomy is uncertain. No evidence regarding comparative efficacy for mortality or colectomy associated with fecal microbiota (Rebyota) can be derived from the clinical trial or open-label extension. Based on clinical expert feedback received for this review, it is plausible fecal microbiota (Rebyota) could result in improvements in mortality and colectomy rates given reductions in rCDI compared with placebo. However, the mortality and colectomy rates from literature cited by the sponsor did not reflect clinical experience in Canada nor published literature conducted in Canada.<br>• The sponsor assumed that patients will only receive 1 dose of fecal microbiota (Rebyota) and will receive subsequent antibiotic treatment if the patient suffers a recurrence. Clinical expert feedback obtained by CDA-AMC indicated that conventional multidose FMT uses more than 1 dose following recurrence. Further, clinical expert feedback indicated that patients who experience a relapse may receive fecal microbiota (Rebyota) as a subsequent treatment. |

| Component | Description |
|---|---|
| | • The patient productivity loss included for the societal perspective is uncertain as the sponsor assumed that patients with active and resolved CDI would be away from work 56 days of an 8-week cycle, and the rate of employment used by the sponsor did not account for the age of the population likely to receive fecal microbiota (Rebyota).<br>• The sponsor's analysis did not include administration costs for fecal microbiota (Rebyota), which was deemed to be unreasonable based on clinical expert feedback received for this review. Patient travel costs associated with the administration of fecal microbiota (Rebyota) were also not considered in the societal perspective. |
| **CDA-AMC reanalysis results** | • CDA-AMC undertook reanalyses to addressed several key limitations, including: assuming that the probability of recurrence after 6 months would not change; adjusting rCDI mortality and the transition probability of rCDI to colectomy health states to reflect clinical practice in Canada; adjusting colectomy mortality; revising antibiotic treatment distribution to reflect treatment received in the PUNCH CD3 trial for no preventive therapy; adding an administration cost for fecal microbiota (Rebyota); and, adjusting calculations informing productivity loss.<br>• Publicly funded health care payer perspective: ICER = $203,679 per QALY gained (incremental costs: $6,328; incremental QALYs: 0.03). A price reduction of 53% corresponding to $4,289 per dose would be required to be considered cost-effective at a WTP of $50,000 per QALY gained.<br>• Societal perspective: ICER = $136,782 per QALY gained (incremental cost: $4,547: incremental QALYs: 0.03). A price reduction of 32% corresponding to $6,205 per dose would be required to be considered cost-effective at a WTP of $50,000 per QALY gained. |

CDA-AMC = Canada's Drug Agency; CDI = *Clostridioides difficile* infection; FMT = fecal microbiota transplant; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; rCDI = recurrent *Clostridioides difficile* infection; vs. = versus; WTP = willingness to pay.

## Budget Impact

CDA-AMC identified several key limitations in the sponsor's analysis:

- The total number of CDI cases is uncertain.
- The proportion of patients who experience a relapse may be overestimated.
- The proportion of patients covered by public drug plans is uncertain and likely underestimated.
- Market uptake is associated with uncertainty.
- Treatment mix of antibiotics for no preventive therapy is associated with uncertainty and likely inappropriate.

CDA-AMC conducted reanalyses including increasing the proportion of patients who are covered under public drug plans; revising the antibiotic treatment distribution; and adjusting the market uptake of fecal microbiota (Rebyota). CDA-AMC reanalyses suggest that reimbursing fecal microbiota (Rebyota) for the prevention of rCDI in adults following antibiotic treatment for rCDI would be associated with a budget impact of $39,889,069 over 3 years (year 1: $13,122,859; year 2: $13,295,593; year 3: $13,470,617).

# Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for fecal microbiota (Rebyota) for the prevention of recurrence of CDI in adults following antibiotic treatment for rCDI. In their request, the sponsor identified the following issues:

- The sponsor expressed concerns regarding the interpretation of the findings; in their view, the overall evidence is suggestive of clinically meaningful effectiveness.
- The sponsor also highlighted the unmet needs in this condition, suggesting that the limitations of conventional FMT have not been fully acknowledged. They also noted that conducting ITCs with other therapies was not feasible.
- The sponsor argued that patients included in the studies were representative of those seen in clinical practice in Canada, especially regarding the antibiotic treatment received for the qualifying episode and the prior number of recurrences.

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- information from the initial submission related to the issues identified by the sponsor
- feedback from 2 clinical specialists with expertise in diagnosing and treating patients with rCDI
- feedback on the draft recommendation from 4 patient groups: the GI Society, the Canadian Digestive Health Foundation, St. Joseph's Healthcare Hamilton, and the Peggy Lillis Foundation
- feedback on the draft recommendation from 8 clinicians or clinician groups: a gastroenterologist and assistant professor of medicine from the University of Ottawa; a physician from Vancouver Coastal Health Authority and University of British Columbia; a physician from the University of Manitoba and Shared Health Manitoba; a physician from Hamilton Health Sciences; Canadian Antimicrobial Resistance Alliance; a physician from the Mayo Clinic; Microbial Health Clinic of the University of Calgary; and a physician from McGill University
- feedback on the draft recommendation from the public drug plans that participate in the reimbursement review process.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

# CDEC Information

**Initial meeting date:** August 27, 2025

## Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, Dr. Ran Goldman, and Dr. Peter Zed.

**Regrets:** Four expert committee members did not attend.

**Conflicts of interest:** None

**Reconsideration meeting date:** September 24, 2025

**Regrets:** Two expert committee members did not attend.

**Conflicts of interest:** None

Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

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**Canada's Drug Agency** (CDA-AMC) is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.



Questions or requests for information about this report can be directed to Requests@cda-amc.ca.