CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

etrasimod (Velsipity)

(Pfizer Canada ULC)

Indication: For the treatment of patients 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or an advanced treatment.

February 12, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting group and all conflicts of interest information from individuals who contributed to the content are included in the posted submission.

Patient Input

Name of Drug: etrasimod (Velsipity™)

Indication: ulcerative colitis

Name of Patient Group: Gastrointestinal Society

Author of Submission: Gail Attara

1. About Your Patient Group

The GI (Gastrointestinal) Society is committed to improving the lives of people with GI and liver conditions, supporting research, advocating for appropriate patient access to healthcare, and promoting gastrointestinal and liver health.

We are a national charity formed in 2008 on the groundwork of its partner organization, the Canadian Society of Intestinal Research (CSIR), which was founded in Vancouver in 1976. We receive national and international attention, simply because we have earned the respect of both the gastrointestinal medical community and Canadians who battle GI and liver issues daily. Our English and French websites received 9,329,479 pageviews in 2023.

All our programs and services focus on providing Canadians with trusted, commercial-free, medically-sound information on gut (including obesity) and liver diseases and disorders in both official languages. Our BadGut® lectures, quarterly *Inside Tract*® newsletter, pamphlets, support groups, and educational videos arm Canadians with the information they require to better understand and manage their specific needs. We also work closely with healthcare professionals and governments at all levels toward system-wide improvements in care and treatment.

2. Information Gathering

The information we used to complete this submission was obtained primarily through questionnaires and interviews:

1. 2015 survey on biologics and biosimilars (then called subsequent entry biologics) completed by 423 Canadians (English: 317 and French: 106) with inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis
2. 2018 survey on the unmet need in IBD completed by 432 Canadians with IBD
3. 2020 survey completed by 579 respondents regarding the unmet needs of IBD
4. 2020 survey on biosimilars with 145 respondents, most of whom had IBD (some had other inflammatory conditions)
5. 2022 survey about the IBD patient journey with 54 Canadian respondents with IBD
6. 2022 focus group with several persons living with IBD so we could map the patient journey and animate it (pictured here), which is available on our website at www.badgut.org/patient-journeys, and we encourage your reviewers to watch these short videos
7. 2023 interviews with seven individuals living with IBD, in both English and French, available on our website at https://badgut.org/ibd-patient-interviews/
8. We also had contact with patients affected by IBD through one-to-one conversations at our BadGut® Lectures, a patient roundtable, recent phone/email/social media interactions with individuals who have IBD, and stories submitted over time from patients.

3. Disease Experience

Ulcerative colitis is an inflammatory bowel disease that can arise at any age, commonly occurring in young people. There is an increased risk for those who have a family member with the condition. Currently, Canada has among the highest prevalence and incidence of IBD yet reported in the world, with approximately 270,000 diagnosed individuals. A recent report from Crohn's and Colitis Canada predicts this to increase to 470,000 Canadians living with IBD by 2035.

Diarrhea, bowel urgency, incontinence, abdominal pain, fever, rectal bleeding, and nausea are common symptoms of ulcerative colitis. Inflammation decreases the intestine's absorptive surfaces, triggering watery stools that can lead to fecal urgency and poor control of bowel function. Low red blood cell count (anemia) can result from blood loss due to ulcerations in the intestine and from general malnutrition due to decreased nutrient absorption and the debilitating effects of the disease.

Some patients have extra-intestinal manifestations, including fever, inflammation of the eyes (uveitis) or joints (arthritis), ulcers of the mouth or skin, tender and inflamed nodules on the shins, and numerous other conditions. Anxiety, stress, and mental health are major factors.

Ulcerative colitis often has a profound effect on an individual's life – physically, emotionally, and socially, both at home and at school or in the workplace. Symptoms can be relentless, embarrassing, and scary. The severity of the disease can fluctuate, making it necessary to go through routine testing, reassessments, and medication changes. It is particularly difficult for children and young adults, since it often affects a person's sense of self.

More than anything, patients have told us that sustained remission/treatment response is more important than relieving any one symptom. As a chronic disease, it is never just one flare that dominates the impact of the disease, but the constant concern that there will be future flares, possibly worse than the last, at unpredictable times, which can disastrously disrupt their lives.
The following quotes are from individuals describing what it feels like during an ulcerative colitis flare, and what their biggest concern is, in their own words:

- "Your gut aches and burns and there is often blood in the toilet. You lose your appetite and weight, unhealthily! **My biggest concern is I'm going to run out of meds to help!"**
- "It's like I can't control anything, I feel weak and can barely get up. My biggest concern is usually when I see blood and determining **at what point to go to the ER**."
- "The **pain is worse than childbirth**... and I have 3 kids...1 labour without drugs."
- "Worst flu symptoms, fatigue, lethargy, like swallowing glass and chili and then having constipation and diarrhea at the same time. Gut cramps and hunger cramps at the same time. **Want to die. Biggest concern is needing a toilet at all times with zero minutes waiting time**."
- "It feels like my guts are in a vise. **The nausea can be so bad I can't move or even vomit and the diarrhea is so painful I'll be literally screaming in the bathroom**."
- "The worst part is fear of **irreversible permanent damage** that will affect your day-to-day life forever."
- "**It is so exhausting and feels like it will never end**. You start to question if you can still live the life you planned. And no-one gives you a break."
- "**A flare can come out of nowhere and completely disrupt your life.** Pain can sometimes be so bad that it keeps you in bed. **You mostly spend life either asleep or on the toilet**. My biggest concern during a flare is being able to keep up with my responsibilities (work, school, social, etc.)."
- "It feels like your body is betraying you. **You can't plan anything in advance because you don't know how your body will feel on a day-to-day basis**."
- "There's a huge element of **fear and worry and being faced with mortality at such a young age**."

It's one thing to read a list of common symptoms or data on how IBD affects patients, but it is the individual stories of these patients, as summarized above, which astound us and motivate us to support patients' need for more diversity in effective treatments. In addition, treatments should improve quality of life, not cause more symptoms, pain, frustration, or hardship.

4. Experiences With Currently Available Treatments

The treatment of ulcerative colitis is multi-faceted; it includes managing the symptoms and consequences of the disease along with therapies targeted to reduce the underlying inflammation. Typically, a patient starts on one type of treatment and, if there is an inadequate response, then switches to another type. Since ulcerative colitis is a chronic disease and there is no cure, it is vital to have a variety of treatment options available.

5-ASA helps to settle acute inflammation and, for some patients, keeps the inflammation inactive when taken on a long-term basis (maintenance). However, this type of medication can have side effects such as headaches, loss of appetite, and nausea. To reduce inflammation in moderate to severe cases, corticosteroids can help but they are not well-tolerated and can have potentially serious side effects, so they are best for short-term treatment only. For topical relief in the colon, corticosteroids are available in rectal

formulations. These are inconvenient therapies that make it difficult for patients to keep a normal routine. Also, if a patient has significant diarrhea, then the rectal medications may be difficult to hold in place for sufficient time to be effective.

Immunosuppressive agents reduce dependence on steroids and can help patients who have steroid-resistant disease, but it could take up to six months or more of therapy to see results. Recent studies have shown that they are not as beneficial as biologics when used on their own, are less effective in healing the mucosa, and can increase the risk of some infections.

Biologics treat ulcerative colitis when older medications fail to relieve symptoms. There are a variety of mechanisms through which they work. On March 29, 2023, the *Institut national d'excellence en santé et en services sociaux* recommended eliminating the requirement of trialing through conventional therapy before patients living with ulcerative colitis can receive biologics. This provides patients with access to more effective tools to tackle this debilitating disease early on in their care. It can also lead to savings in healthcare resources. We applaud this recommendation and encourage all jurisdictions in Canada to follow.

There are also newer classes of medications. These are Janus kinase (JAK) inhibitors and sphingosine-1-phosphate (S1P) inhibitors. JAK inhibitors typically work faster than other immunosuppressive medications, pose no risk for immunogenicity, unlike biologics, and are easier and more convenient to take since they are in pill form. We are also aware of many recent health risks that have arisen with the first product of this type introduced to the market. However, upadacitinib (Rinvoq®) works in a more targeted way, which might mitigate the side effects found with other JAK inhibitors.

For S1P inhibitors, there is currently only one drug in this class, ozanimod (Zeposia®). It treats moderate-to-severe ulcerative colitis and may not be available for those with contraindications of poorly controlled diabetes or heart block. However, the approval of etrasimod, another S1P inhibitor, gives patients another treatment option in this class of medication.

While there are options available, patients still have a lot of difficulty obtaining remission or adequate symptom relief. Some patients have shared their fears about running out of different treatments to try, if the current medication they are on stops working. In one of our surveys, we asked patients if the currently available medications are adequate to control their disease. Only 24% of those with IBD thought that the available medications are adequate, 56% found them to be only somewhat adequate, and 20% not at all adequate. Patients are still suffering, and they need new and effective options to achieve mucosal healing and reduce the debilitating symptoms of ulcerative colitis.

Medications help avert removal of all or part of the colon. Since ulcerative colitis is a systemic disease, not only the colon is involved. Therefore, if a surgeon removes the colon (colectomy) and then brings the end of the remaining intestine through a new surgical opening in the abdominal wall (ostomy) to which the patient can attach a removable appliance to collect stool, the patient still experiences symptoms. With the loss of colon function, bowel movements can occur frequently and have high liquid content. Another surgical treatment is to remove diseased tissue and create a pouch from remaining tissue so defecation can occur via the rectum. However, one complication that can occur is pouchitis, which is inflammation within the surgically created pouch. This means that even after surgery, patients could face troublesome gastrointestinal symptoms. Living without your colon is very difficult.

5. Improved Outcomes

Patients affected by ulcerative colitis need access to medications that work. Inadequate access to medication results in preventable patient suffering (e.g., continual, debilitating disease symptoms; secondary illnesses such as depression and anxiety disorders; and loss of family/social interactions). It also leads to unnecessary usage of healthcare resources (e.g., hospital stays, surgeries, diagnostic procedures, other medications) and a ripple effect of financial burden on the government and taxpayers (e.g., through inability to work, long-term disability claims, biologic-related debt, and even bankruptcy).

When the ulcerative colitis patient receives the right medication at the right time and for the right duration – as determined between physician and patient – these individuals can live full, rewarding lives as productive, valuable citizens who participate in the workforce and community. However, since patients are unique, they respond differently to various medications, and in some cases stop responding to medications after using them for some time, so it is important to have a variety of options available.

6. Experience With Drug Under Review

We have not interviewed patients that have experience with etrasimod. However, patients have told us that they want more options, particularly those that are accessible. This includes medications that are in pill form, such as etrasimod,[1] or subcutaneous injections,

allowing individuals to take their medicines at home and not have to request time off work/school, which can lead to lost wages and/or productivity. While biologic medications are very effective, the injections or infusions required are a lot of work and effort, especially for those with a chronic disease. However, what's most important for patients is having timely access to a variety of treatment options that they, along with their treating physician, can choose from to determine the best medication that fits their needs.

7. Companion Diagnostic Test

n/a

8. Anything Else?

n/a

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No.

1. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No.

2. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Pfizer				x

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Gail Attara
Position: President and Chief Executive Officer
Patient Group: Gastrointestinal Society
Date: 2024-02-09

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[1] Sandborn WJ et al. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies. The Lancet. 2023;401:1159-1171. https://doi.org/10.1016/S0140-6736(23)00061-2.

Name of Drug: Velsipity (etrasimod)
Indication: Ulcerative colitis
Name of Patient Group: Crohn's and Colitis Canada
Author of Submission: Patrick Tohill

1. About Your Patient Group

Describe the purpose of your organization. Include a link to your website.

Crohn's and Colitis Canada website (https://crohnsandcolitis.ca/)

Crohn's and Colitis Canada is the only national, volunteer-based health charity focused on finding the cures for Crohn's disease and ulcerative colitis, the two main forms of inflammatory bowel disease (UC), and improving the lives of children and adults affected by these diseases.

Crohn's and Colitis Canada is one of the top health charity funders of Crohn's and colitis research in the world, investing over $140 million in research since our founding in 1974. The organization also delivers on its promise through patient programs, advocacy and awareness. We help improve the quality of lives today by:

- Sharing accurate and reliable information on treatments, research and issues related to life with Crohn's and colitis through website, print materials, webinars and live events;
- Increasing public washroom access through the GoHere program;
- Raising awareness about these Canadian diseases with bilingual public communication;
- Offering kids with Crohn's or colitis camp experience;
- Providing a peer support program to newly diagnosed people; and
- Advocating on behalf of the patients and caregivers on priority concerns and needs.

Crohn's and Colitis Canada is comprised of approximately 65,000 supporters including volunteers, donors or individuals interested in engaging with the organization. There is no paid membership. Crohn's and Colitis Canada is governed by a national volunteer Board of Directors. The organization has a network of volunteer-led Chapters in 46 communities across the country, offering information, events, fundraising opportunities and encouragement. There are thousands of volunteers from coast-to-coast supporting Crohn's and Colitis Canada's mission.

2. Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include **when** the data were gathered; if data were gathered **in Canada** or elsewhere; demographics of the respondents; and **how many** patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

Information summarized in this submission was compiled from two online surveys undertaken in 2022 and a phone interview with a patient with ulcerative colitis. We were unable to connect with any patients who participated in the etrasimod clinical trial but would still like to share our perspectives on disease experience, experience with other therapies, unmet needs, etc.

Survey 1: Our first survey was deployed to our community to better understand unmet needs and priority concerns. The survey included responses from 1706 Canadians, of which 354 had moderate to severe ulcerative colitis.

Survey 2: The second survey, also deployed in 2022, captures the experience of four ulcerative colitis patients, including two that were taking another oral therapy (Rinvoq) as part of a clinical trial.

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

The results from the Unmet Needs survey (Survey 1) provide a window into how moderate to severe ulcerative colitis (UC) patients live and manage their symptoms.

When asked what UC related complications they are experiencing currently or within the past year, most frequently reported were mental health and stress (65%), followed by joint inflammation & arthritis (51%), anal fissures and hemorrhoids (40%), anemia (33%), and skin conditions and malnutrition and weight loss both at ~ 30%. Other complications include strictures, adhesions (scar tissue), bowel obstruction, eye inflammation, perianal or anal fistulas and abscesses, internal (or intraabdominal) fistulas or abscesses, stricture, ankylosing spondylitis (arthritis of the spine), liver conditions, and cancer. 13% of the respondents were currently experiencing at least one complication of UC.

Thinking back to when they were first diagnosed, patients noted that they hid aspects of their diagnosis from friends, coworkers and classmates. There is a general misunderstanding of what UC is, which could impact how patients navigate social situations. Nine-in-ten agree that most people don't know what UC is. This is further compounded by the fact that almost two thirds (63%) of patients agree that their family and friends don't understand what they are going through. In spite of their medications, two thirds of the patients continue to experience at least one symptom of UC, the most frequent of which are bloating and urgent and frequent need to use the washroom. **Over half (56%) believed that different treatment options could make them feel better.** At least half of patients felt they could not be open about their UC, felt isolated due to their UC, and believe that their UC has had a negative impact on their romantic relationships with their spouse or partner.

A significant proportion of patients have adjusted their lifestyle and expectations. 72% agreed that they have changed the expectations they had of themselves or that they are always adapting their lifestyle to account for their UC. Two in five patients reported that they changed their travel plans and one in five changed their career aspirations.

Ulcerative colitis affects every aspect of a person's life from family, friends and work activities. Due to unpredictable urgency of bowel movements, accidents are not uncommon, especially when patients are experiencing flares. Patients often hide their disease from work colleagues, friends (35%) and even relatives because of the perceived stigma of the condition being a "poop" disease. Unable to predict when their next flare will occur and how to control their flare, isolation, stress and anxiety are companions to the patient's disease journey.

At least half of patients felt they could not be open about their UC, felt isolated due to their UC, and believe that their UC has had a negative impact on their romantic relationships with their spouse or partner.

Those patients we surveyed / interviewed who had experience with oral medications preferred this type of treatment. Patients noted the convenience of pill-based administration, not needing to worry about refrigerating the medication and not having to travel to a clinic for infusions. One patient described the switch to an oral therapy as having been "amazing" in terms of its impact on quality of life, adding: *"Being hooked up to an IV for six hours, no thank you. Injecting yourself with biologics, no thank you."*

4. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

Disease management is incredibly important to ensuring patients can live a life of normalcy. In our 2022 survey, most patients reported having used a combination of medications to manage their UC, with systemic steroids (79%), sulfasalazine & 5Aminosalicylates (76%) and biologics

(57%) being most common among those with ulcerative colitis, followed by immunomodulators (45%), antibiotics (42%), and non-systemic steroids (38%).

Importantly, the severity of their IBD plays an important role in deciding which medications are being used. Those who described their condition as moderate to severe were more likely to have used almost all medications asked except immunomodulators, which is more commonly used by patients who have a severe state.

More than one in five are currently taking steroids (30% within last year). Roughly one third of the UC patients have also tried medical cannabis, anti-anxiety medications, and antidepressants to manage their symptoms.

Steroid use is also an important aspect in symptom management and patients aren't particularly supportive of this treatment option. Almost all patients surveyed agree that they only take systemic steroids if absolutely necessary (93%) with four in five in agreement that they wish they could eliminate systemic steroids from the list of medications they use.

Half of respondents say that systemic steroids is/was a burden in their UC management. This is particularly true among those with moderate to severe forms of UC, and among women. Those under the age of 55 are more likely to agree that they have had side effects from systemic steroids. Those with a severe state of UC indicate that they have also experienced side effects from systemic steroid use (90%).

Among those who are using steroids 84% have been on systemic steroids for less than 12 months; with 42% less than three months; and 13% of the respondents having been on steroids for over a year. Two thirds of the respondents feel that systemic steroids are a burden to their UC treatment, with 71% indicating that they have experienced side effects of the steroids.

Among patients who say managing medication use is important, having enough of their treatment options, understanding side effects, and minimizing steroid use were most important. Women are more likely than men to find it important to ensure they have enough treatment options, understand the side effects of long-term use, and minimize the use of steroids.

5. Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

Patients seek any treatments that can mitigate these symptoms to protect a patient's ability to work productively, attend school and social events, and even basic daily necessities like leaving the house to run errands or have the energy to maintain a household or raise children. Quality of life could be greatly improved in UC patients if their flares are brought into remission. Based on our survey results, the majority of patients with moderate to severe UC continue to experience symptoms with current treatment options.

6. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways? If applicable, please provide the sequencing of therapies that patients would have used prior to and after in relation to the new drug under review. Please also include a summary statement of the key values that are important to patients and caregivers with respect to the drug under review.

The clinical trial involved very few Canadians and we were unable to identify a patient to interview with experience of the study drug.

7. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Consider:

- Access to testing: for example, proximity to testing facility, availability of appointment.
- Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?
- Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?
- How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.

The clinical trial involved very few Canadians and we were unable to identify a patient to interview with experience of the study drug.

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

Patients and clinicians need a range of options so that the right treatment can be prescribed to the right patient at the right time. It's time to rethink requirements that force patients to try and fail multiple therapies before they can be reimbursed for advanced therapies that their physician might otherwise have prescribed as a first line option.

Appendix: Patient Group Conflict of Interest Declaration

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1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   The first survey was conducted in collaboration with Leger who performed the initial analysis of the data.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

   Crohn's and Colitis Canada receives grants, sponsorships and scholarship funding from pharmaceutical companies involved in the treatment of Crohn's disease and ulcerative colitis. These funds are used to sponsor patient education events, community programs, research grants,

research and medical conferences, educational brochures, kid's camps, post-secondary scholarships as well as outreach and advocacy activities on behalf of Canadians living with Crohn's and colitis. The vast majority of Crohn's and Colitis Canada's funding comes from individual donors contributing to fundraising events such as the Gutsy Walk. Crohn's and Colitis Canada is participating in this review as part of our advocacy for Canadians living with inflammatory bowel disease and does not endorse or recommend the use of specific products or treatment or attribute of any product. No sponsor was involved in developing the content of this submission.

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Pfizer				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: **Patrick Tohill**

Position: **Director, Advocacy and Government Affairs**

Patient Group: **Crohn's and Colitis Canada**

Date: **February 2, 2024**

Clinician Input

CADTH Project Number: SR0795-000

Generic Drug Name (Brand Name): Etrasimod (Velsipity)

Indication: Ulcerative Colitis

Name of Clinician Group: Canadian IBD Interest Group

Author of Submission: John K. Marshall MD MSc FRCPC AGAF

1. About Your Clinician Group

The Canadian IBD Interest Group is an ad hoc assembly of academic and community gastroenterologists from across Canada with a common interest and subspecialty expertise in the management of inflammatory bowel disease (IBD). As new highly effective and well tolerated therapies become available for management of both Crohn's disease (CD) and ulcerative colitis (UC), members of this group have expressed a common interest in advocating on behalf of patients to identify and address unmet clinical needs.

2. Information Gathering

Members of the group participated in a virtual meeting on December 18 2023 to discuss the UC treatment landscape and emerging therapies. In this context, efficacy and safety data from the etrasimod development program were reviewed. Members considered these data in the context of their clinical experience and expert opinion to identify how access to therapy could address unmet needs and improve patient outcomes. Current therapies, therapeutic goals, and patient preferences were all considered in the discussion. Recent literature was reviewed, as were data from the etrasimod clinical development program.

3. Current Treatments and Treatment Goals

CD and UC are chronic inflammatory disorders of the gastrointestinal tract [Gros 2023]. The inflammation of UC is limited to the colon, always involving the rectum and extending proximally to a variable extent. Patients with UC can experience periods of increased disease activity ("flares") and periods when disease is under relative control. When active, UC can cause diarrhea, urgency, pain, fever and rectal bleeding. Severe or fulminant UC is a medical emergency, typically requiring hospitalization. Over the long term, poorly controlled UC is associated with an increased risk of colorectal cancer. Surgical intervention for severe or refractory ulcerative colitis entails colectomy with either a permanent end ileostomy or construction of an ileoanal pouch. Although effective, the latter does not allow return to normal quality of life with high stool frequency, frequent fecal soiling and fixed risks of female infertility and chronic pouchitis. Accordingly, colectomy should not be considered curative.

As emphasized in the recent STRIDE consensus guidelines [Turner 2021], treatment goals in managing UC include both improvement in symptoms and improvement in objective markers of disease activity. There can be a disconnect between symptom severity and underlying disease activity, with the latter much more predictive of the future disease course. Objective measures of disease activity include endoscopic and histologic assessment, as well as biomarkers such as fecal calprotectin (FC) and serum C reactive protein (CRP).

For mild to moderate ulcerative colitis, oral and/or rectal 5-aminosalicylates (5-ASA) are considered a first line therapy [Bressler 2015; Gros 2023]. Systemic corticosteroids are reserved for 5-ASA failure or for first-line treatment of moderate to severe disease. Patients who require systemic corticosteroids, and particularly those who with steroid-refractory or steroid-dependent disease will transition to an advanced therapy. Advanced therapies include both biologics (adalimumab, infliximab, golimumab, vedolizumab, ustekinumab, mirikizumab) and oral small molecules (tofacitinib, upadacitinib, ozanimod). Thiopurines are now less often used for treatment of UC due to their limited efficacy and long-term safety concerns [Chhibba 2020].

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

There remains a significant unmet need with respect to the overall efficacy of existing therapies for ulcerative colitis. Although highly effective for many patients, each of our current advanced therapies still only yields long-term remission in a minority [Kayal 2023]. Biologic therapies such as infliximab are associated with high rates of both primary non-response and secondary loss of response [Savelkoul 2023]. To manage such treatment failure, dose escalation is common and further increases drug costs [Savelkoul 2023]. More therapies with novel mechanisms of action are needed.

Most IBD patients prefer orally administered therapies and many are reluctant to initiate biologic agents that require parenteral (i.e. subcutaneous or intravenous) delivery [Buisson 2023; Denesh 2021]. Oral small molecules have more predictable pharmacokinetics than monoclonal antibodies. Oral therapies also avoid the cost, travel requirements and infrastructure of intravenous infusions and/or subcutaneous injection training. Long-term parenteral delivery of maintenance therapy for UC can be stigmatizing for many young patients. There is a need for oral therapies that are well tolerated and provide durable disease control. As noted below, etrasimod offers safety advantages over other existing orally administered advanced therapies for ulcerative colitis.

UC patients with disease limited to the rectum (i.e. ulcerative proctitis) have previously been excluded from clinical development programs, yet represent up to 30 per cent of the overall UC population. Over time, ulcerative proctitis can extend more proximally in the colon, and can require surgical and advanced medical therapy almost as often as more extensive disease [Hochart 2017]. A recent expert consensus statement from the International Organization for the Study of IBD (IOIBD) proposed a framework for their inclusion in future clinical trials [Caron 2022]. To date, only trials of 5-ASA and corticosteroids have been studied and demonstrated efficacy in this important patient subgroup [Aruljothy 2023].

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

The mechanism of action of etrasimod is familiar to clinicians, as another S1P receptor modulator (ozanimod) has already been approved for treatment of UC. Etrasimod offers specific advantages over ozanimod including: (1) a shorter half-life; (2) no requirement for initial dose titration and (3) fewer drug-drug interactions (for example, use of MAO inhibitors is contraindicated with ozanimod but not with etrasimod). For these reasons, the expected approval of etrasimod is seen favourably by clinicians.

As a small molecule therapy, etrasimod is administered orally. The only other class of oral small molecule advanced therapies approved for treatment of ulcerative colitis is the JAK inhibitors (tofacitinib and upadacitinib). While highly effective, JAK inhibitors have been associated with fixed and continuing long-term risks of infection, major adverse cardiovascular events, venous thromboembolism and malignancy. JAK inhibitors should used with caution in patients at increased risk of these adverse effects, and these risks have limited their uptake by physicians and patients. The long-term safety profile of SIP receptor modulators appears to be more favourable.

As a convenient and well-tolerated oral therapy, the Group felt that etrasimod is likely to be used most often as a first-line advanced therapy, after failure of conventional therapies that would include 5-ASA and/or corticosteroids. However, etrasimod appears also to be effective after failure of another advanced therapy, and could also be used as a second- or third-line advanced therapy in selected cases. Indeed, the efficacy of etrasimod appears to be superior to that of ozanimod in patients who have already failed another advanced therapy. Oral therapies avoid the cost, travel requirements and infrastructure of intravenous infusions and/or subcutaneous injection training. Oral therapies are also generally preferred by patients [Buisson 2023; Denesh 2021].

Of note, the etrasimod clinical development program was the first to include patients with ulcerative proctitis, and showed efficacy in that important and neglected subset of patients. Accordingly, etrasimod may be positioned as a first-line advanced therapy for patients with ulcerative proctitis. who despite limited disease extent have frequently symptoms of urgency, incontinence, and rectal bleeding and substantial unmet medical needs.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

As noted above, it is anticipated that etrasimod is likely to be used most often as a first-line advanced therapy, but could also be used as a second- or third-line agent in selected cases. Etrasimod has not been evaluated for use in patients with fulminant or hospitalized UC, and so its use would be unlikely in that setting. Etrasimod will be an appealing option for patients who prefer orally administered therapy, and who are reluctant or unwilling to accept parenterally administered biologic therapies. As also noted above, etrasimod is the first advanced therapy to show efficacy in patients with ulcerative proctitis, and hence would likely be used as a first-line advanced therapy in this subgroup.

Unfortunately, there are no reliable predictors of response that are unique to this agent and no available companion diagnostic test has been developed.

Misdiagnosis of active ulcerative colitis is unlikely, as it is common practice to assess both symptoms and objective measures of disease activity (e.g. fecal calprotectin and/or serum c-reactive protein and/or endoscopy with biopsy) before initiating therapy with etrasimod or any other advanced therapy. As delayed diagnosis of inflammatory bowel disease is common, it can present at an advanced stage, requiring early access to advanced therapy [Jayasooryia 2023].

Overall, the Group felt that the advantages of etrasimod included: (1) oral delivery; (2) a once-daily dosing regimen; (3) efficacy in all patient subgroups including those with limited proctitis; and (4) a favourable long-term safety compared to existing oral alternatives including ozanimod, upadacitinib and tofacitinb.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

A combined assessment of both symptoms and objective measures of disease activity is recommended in the recent STRIDE consensus [Turner 2021]. Objective measures, and in particular endoscopic disease activity, are considered to be the most useful predictors of subsequent disease activity.

The ELEVATE-UC clinical trial used a treat-through design. Its co-primary endpoints were clinical remission at weeks 12 and 52. Clinical remission was defined as a composite of stool frequency subscore = 0 (or stool frequency subscore = 1 with a ≥1-point decrease from baseline), rectal bleeding subscore = 0, and endoscopic subscore of 1 or less by independent, centrally read assessment (without friability). This aligns well with STRIDE criteria by combining symptoms (rectal bleeding and stool frequency) with an objective measure of disease activity (endoscopy). In practice, a meaningful improvement in symptoms would be expected by week 12 and this should be accompanied by a decrease in biomarkers (C-reactive protein or fecal calprotectin). Although ELEVATE-UC demonstrated an endoscopic response at week 12, the Group would not usually assess endoscopic activity until month 6 to 12.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Either failure of efficacy or a significant adverse effect would provide reason to discontinue etrasimod. An inadequate clinical response within 12-16 weeks of starting therapy would warrant consideration of treatment withdrawal. **DEFINE RESPONSE** However there is often a disconnect between symptoms of IBD and the severity inflammation. As such, assessment of treatment response should include both assessment of symptoms and objective biomarkers of disease activity. True failure of induction therapy would warrant a switch to another advance therapy with a different mechanism of action.

Adverse effects of therapy could also warrant discontinuation of etrasimod, but these are anticipated to be uncommon. Patients starting etrasimod would be screening for eligibility according to risk factors for cardiac and retinal adverse effects, and most adverse effects are limited to the first few days of induction therapy. Potential patients noted to be at increased risk of adverse effects can be further screening by baseline electrocardiography or retinal imaging, and consultation with a cardiologist or vision care professional. Concurrent medications should also be screened for potential drug-drug interactions. Overall, the Group felt that the safety profile of etrasimod among patients who pass a screening assessment appears to be excellent.

5.5 What settings are appropriate for treatment with etrasimod? Is a specialist required to diagnose, treat, and monitor patients who might receive etrasimod?

It is anticipated by this Group that etrasimod will be prescribed by physicians experienced in the management of UC, and most often by gastroenterologists or general internists with specific training and experience. As an oral therapy, etrasimod would be

administered at home. The rare patients who require first-dose monitoring would need to receive that dose under supervision in an ambulatory clinic setting. However no such infrastructure would be required for subsequent doses. Specialist monitoring will be required to assess response to therapy by symptoms, biomarkers and endoscopy, and this follow-up would most often be delivered by gastroenterologists. The frequency of follow up would be individualized to patient requirements and practice setting. However response to induction therapy would typically be assessed 12 to 16 weeks after starting therapy, with assessment of biomarkers at 3-6 months and endoscopy at 6-12 months in accordance with STRIDE guidelines. Of course, earlier assessment would be provided in the event of worsening symptoms or possible adverse effects of therapy (Turner 2021).

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6. Additional Information

None

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

3. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No guidance or support was provided by any public or private interest.

4. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No assistance was provided by any public or private interest.

5. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: John Marshall

Position: Professor of Medicine, McMaster University

Date: 14-11-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie				X
Alimentiv		X		
Amgen		X		
Bausch Health	X			
Bristol Myers Squibb		X		
Celltrion		X		
Ferring		X		
Fresenius Kabi	X			
Janssen			X	
Lilly		X		
Lupin	X			
Organon	X			
Pfizer			X	
Pharmascience	X			
Roche	X			
Sandoz	X			
Takeda			X	
Teva	X			
Viatris	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Marc Bradette

Position: Clinical Professor of Medicine, Universite de Laval

Date: 14-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AbbVie		X		
Takeda		X		
Pfizer		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Jeff McCurdy

Position: Associate Professor of Medicine, University of Ottawa

Date: 14-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie			X	
Amgen	X			
BMS	X			
Fresenius Kabi	X			

Janssen		X		
Pfizer		X		
Takeda			X	
Lilly	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Neeraj Narula

Position: Associate Professor of Medicine, McMaster University

Date: 14-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie			X	Q
Janssen		X		
Takeda		X		
Lilly	X			
Fresenius Kabi	X			
Pfizer		X		
Viatris	X			
Sandoz	X			
Iterative Health			X	
Innomar Strategies		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Christopher Ma

Position: Associate Professor of Medicine, University of Calgary

Date: 14-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AbbVie				X
Alimentiv				X
Amgen			X	
AVIR Pharma		X		
BioJAMP		X		
Bristol Myers Squibb		X		
Celltrion		X		
Ferring				X
Fresenius Kabi			X	
Janssen			X	
McKesson		X		
Mylan		X		
Pendopharm		X		
Pfizer				X
Prometheus Biosciences Inc.		X		
Roche		X		
Sanofi			X	
Springer Publishing			X	

Takeda			X	
Tillotts Pharma		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Laura Targownik

Position: Professor of Medicine, University of Toronto

Date: 14-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Janssen		X		
Abbvie			X	
Takeda		X		
Pfizer			X	
Amgen	X			
Fresenius Kabi	X			
Organon	X			
Lilly		X		
Bristol Myers Squibbq		X		
Viatris	X			
Celltrion	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Vipul Jairath

Position: Professor of Medicine, Western University

Date: 14-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 7

Company	**Check appropriate dollar range***			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie			X	
Alimentiv			X	
Arena	X			
Asahi Kasei	X			
Asieris	X			
AstraZeneca	X			
Avoro Capital	X			
Bristol Myers Squibb		X		
Celltrion	X			
Lilly		X		
Endpoint Health	X			
Ferring	X			
Flagship Pioneering	X			
Fresenius Kabi	X			
Galapagos	X			
Gilde Healthcare	X			
Glaxo-Smith-Klein	X			
Genentech	X			

Gilead	X			
Janssen			X	
Merck	X			
Mylan	X			
Metacrine	X			
Pandion	X			
Pendopharm	X			
Pfizer			X	
Protagonist Therapeutics	X			
Reistone Biopharma	X			
Roche	X			
Sandoz	X			
Second Genome	X			
Sorriso	X			
Takeda			X	
Teva	X			
Topivert	X			
Ventyx	X			
Vividion	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Yvette Leung

Position: Assistant Clinical Professor of Medicine, University of British Columbia

Date: 14-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 8

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AbbVie			X	
Pfizer			X	
Takeda			X	
Janssen			X	
Lilly			X	
Celltrion	X			
Sandoz	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 9

Name: Edmond-Jean Bernard

Position: Associate Professor of Medicine, Universite de Montreal

Date: 14-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 9

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AbbVie		X		
Janssen		X		
Pfizer		X		
Takeda	X			

Lilly	X			
Fresenius Kabi	X			
Sandoz	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 10

Name: Charles Bernstein

Position: Professor of Medicine, University of Manitoba

Date: 14-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 10

Company	**Check appropriate dollar range***			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Pfizer	X			
Abbvie	X			
Sandoz	X			
Janssen		X		
Lilly	X			
Bristol Myers Squibb	X			
Takeda	X			
Pendopharm	X			
Amgen	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 11

Name: Mark MacMillan

Position: Associate Professor of Medicine, Dalhousie University

Date: 14-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 11

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie		X		
Janssen	X			
Fresenius Kabi	X			
BioJAMP	X			
Organon	X			
Pendopharm	X			
Pfizer	X			
Takeda	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 12

Name: Robert Battat

Position: Assistant Professor of Medicine, Universite de Montreal

Date: 14-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 12

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Janssen			x	
Abbvie			x	
Takeda			x	
Pfizer			x	
Bristol Myers Squibb			x	
Eli Lilly	x			
Prometheus Laboratories		x		

* Place an X in the appropriate dollar range cells for each company.