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CADTH Reimbursement Recommendation

Etrasimod (Velsipity)

Indication: For the treatment of adults 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

Sponsor: Pfizer Canada ULC

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Velsipity?

CADTH recommends that Velsipity be reimbursed by public drug plans for the treatment of adults with moderately to severely active ulcerative colitis (UC) whose disease had an inadequate response or lost response, or who were intolerant, to either conventional therapy or an advanced treatment, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Velsipity should only be covered to treat adults with moderately to severely active UC whose disease has had an inadequate response or lost response, or who were intolerant, to either conventional therapy or an advanced treatment provided that it is covered for a similar patient population and in a similar way to other advanced therapies for UC (e.g., biologics, sphingosine 1-phosphate receptor modulators, or Janus kinase [JAK] inhibitors) currently reimbursed by public drug plans.

What Are the Conditions for Reimbursement?

Velsipity should only be reimbursed if it is prescribed by a physician experienced in the diagnosis and management of UC, if it is not used in combination with other advanced therapies for UC, and if the cost is reduced so that it does not cost the drug programs more than the least costly relevant advanced therapy. A patient's disease must respond to the treatment in the first 12 weeks of starting Velsipity to continue receiving the drug.

Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that more patients treated with Velsipity showed clinical remission and endoscopic improvement than patients treated with placebo and this benefit was maintained for up to 1 year.
- Velsipity may meet some of the needs identified as important to patients, including being an additional treatment option that can improve symptoms and is easy to take. Additionally, more patients treated with Velsipity had corticosteroid-free clinical remission than those treated with placebo, and reducing reliance on systemic corticosteroids is important to patients and clinicians.
- Based on CADTH's assessment of the health economic evidence, Velsipity does not represent good value to the health care system at the public list price. The committee determined that there is not enough

Summary

evidence to justify a greater cost for Velsipity than other advanced therapies reimbursed for the treatment of adults with moderately to severely active UC.

- Based on public list prices, Velsipity is estimated to save the public drug plans approximately $6 million over the next 3 years. However, the actual budget impact is uncertain and is likely to be affected by the prices of advanced therapies for UC paid by the public drug plans.

Additional Information

What Is UC?

UC is an inflammatory bowel disease that causes inflammation and ulcers in the lining of the large intestine and rectum. Signs and symptoms include blood in stool, frequent diarrhea, loss of appetite, the strong urge to use the bathroom without necessarily having a bowel movement, abdominal pain, and rectal bleeding. UC occurs in 414 per 100,000 people in Canada.

Unmet Needs in UC

The available treatment options do not work in all patients with UC. Treatment response varies across patients and response to treatment may stop after prolonged use; thus, patients have noted a need for other treatments that reduce the severity of symptoms, demonstrate good tolerability, improve quality of life and work productivity, and have satisfactory convenience and feasibility.

How Much Does Velsipity Cost?

Treatment with Velsipity is expected to cost approximately $15,742 per patient per year.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that etrasimod be reimbursed for the treatment of adults with moderately to severely active UC whose disease has had an inadequate response or lost response, or who were intolerant, to either conventional therapy or an advanced treatment only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 2 phase III, randomized, double-blind, placebo-controlled trials (ELEVATE UC 12, N = 354, and ELEVATE UC 52, N = 433) demonstrated that treatment with etrasimod results in added clinical benefit in adults with moderately to severely active UC. A greater proportion of patients in the etrasimod group than in the placebo group had clinical remission at 12 weeks and 52 weeks. The between-group common risk differences were 9.7% (95% confidence interval [CI], 1.1% to 18.2%; P = 0.026) and 19.8% (95% CI, 12.9% to 26.6%; P < 0.001) at 12 weeks in the ELEVATE UC 12 and ELEVATE UC 52 trials, respectively, and 25.4% (95% CI, 18.4% to 32.4%; P < 0.001) at 52 weeks in the ELEVATE UC 52 trial. In addition, greater proportions of patients in the etrasimod group had endoscopic improvement compared with the placebo group at week 12 (ELEVATE UC 12: between-group difference 12.1%; 95% CI, 3.0% to 21.2%; P = 0.009, and ELEVATE UC 52: 21.2%; 95% CI, 13.0% to 29.3%; P < 0.001) and at week 52 (ELEVATE UC 52: between-group difference 26.7%; 95% CI, 19.0% to 34.4%; P < 0.001). Similarly, there were statistically significant and clinically meaningful between-group differences in favour of the etrasimod group, compared to placebo, for mucosal healing, sustained clinical remission, corticosteroid-free clinical remission, clinical response, and symptomatic remission at 12 and 52 weeks.

Patients indicated a need for new and effective treatment options to reduce symptoms and achieve sustained remission because patients' disease may not have a response or may lose response to currently available treatment options. In addition, patients identified the need to reduce reliance on systemic corticosteroids and have treatment options that are easy to take (i.e., reduce the burden of administration). Etrasimod may address some of these unmet needs, such as sustained clinical remission and corticosteroid-free clinical remission, and is a once-daily oral medication.

At the sponsor-submitted price for etrasimod and publicly listed price for comparators, etrasimod was more costly than the least costly advanced therapy for adults with moderately to severely active UC. Direct comparative evidence to other advanced therapies was not identified and indirect evidence suggests that [redacted]. As such, the total drug cost of etrasimod should not exceed the total drug cost of the least costly relevant advanced therapy reimbursed in this patient population.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Eligibility for reimbursement of etrasimod should be based on the criteria used by each of the public drug plans for the reimbursement of other advanced drugs for the treatment of moderately to severely active UC for those whose disease has had an inadequate response or lost response, or who were intolerant, to either conventional therapy or an advanced therapy.	The ELEVATE UC 12 and ELEVATE UC 52 trials demonstrated that etrasimod has a clinical benefit in patients with moderately to severely active UC whose disease has had an inadequate response or lost response, or who were intolerant, to at least 1 the following therapies: conventional therapy (e.g., corticosteroids, thiopurines), biologic therapy, or JAK inhibitor therapy. The indirect evidence suggests there may be no meaningful difference between etrasimod and other advanced therapies.	The definitions of moderately to severely active UC and inadequate response, intolerance, or loss of response to other therapies should align with those used for other reimbursed advanced therapies. Advanced therapies include biologics, JAK inhibitors, and sphingosine 1-phosphate receptor modulators.
Renewal		
2. The patient must have achieved clinical response to therapy after 12 weeks of treatment initiation to continue therapy.	This is to ensure patients are benefiting from etrasimod therapy. The ELEVATE UC 12 trial assessed the efficacy and safety of etrasimod after 12 weeks of treatment. The ELEVATE UC 52 trial assessed efficacy and safety after 12 weeks of treatment, then patients continued into an additional 40-week treatment period.	A modified Mayo score was used in the ELEVATE UC 12 and ELEVATE UC 52 trials to determine clinical response and remission. However, CDEC considered the invasive nature of an endoscopy and the limitations associated with timely access and associated costs of health care resources in Canada. Ultimately, CDEC considered it appropriate to leave the determination of clinical response up to the judgment of the treating physician.
3. Assessment for renewal after the first assessment of treatment response should be performed every year. The patient's disease must maintain clinical response to therapy for them to continue receiving etrasimod.	Patients whose disease loses response to etrasimod are no longer benefiting from treatment.	—
Prescribing		
4. Etrasimod should only be prescribed by a physician experienced in the diagnosis and management of UC.	This ensures that etrasimod is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
5. Etrasimod should not be reimbursed when used in combination with other advanced therapies for UC, such as biologics, sphingosine 1-phosphate receptor modulators, or JAK inhibitors.	There is no evidence to support the use of etrasimod in combination with a biologic therapy, JAK inhibitor, or other sphingosine 1-phosphate receptor modulator for UC.	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
6. Etrasimod should be negotiated so that it does not exceed the drug program cost of treatment with the least costly relevant advanced therapy reimbursed for the treatment of moderately to severely active UC.	Indirect evidence [redacted]. As such, there is insufficient evidence to justify a cost premium for etrasimod over the least costly relevant advanced therapy reimbursed for this indication.	–

CDEC = Canadian Drug Expert Committee; JAK = Janus kinase; UC = ulcerative colitis.

Discussion Points

- CDEC discussed that the evidence from the ELEVATE UC 12 and ELEVATE UC 52 trials was of high certainty, per the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessment that etrasimod results in a clinically important improvement for the outcomes of endoscopic improvement, mucosal healing, clinical remission, sustained clinical remission, corticosteroid-free clinical remission, symptomatic remission, and clinical response when compared with placebo. There was evidence of moderate certainty that etrasimod likely results in little to no difference in serious treatment-emergent adverse events (TEAEs) at 12 weeks and 52 weeks compared to placebo.
- Patients described many of the significant negative impacts of UC on quality of life, as well as its effect on participation at school or in the workplace. Health-related quality of life (HRQoL) evidence from the ELEVATE 12 UC and ELEVATE 52 UC trials as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) was of moderate and low certainty at 12 weeks and 52 weeks, respectively, based on the GRADE assessment. Although the patients in the etrasimod group reported greater improvement from baseline than those in the placebo group at 12 weeks and 52 weeks, the between-group differences in IBDQ change at both time points were not considered clinically meaningful. In addition, the HRQoL end points were not controlled for multiplicity.
- CDEC noted that etrasimod is a treatment option for patients who have experienced loss of response, inadequate response, or were intolerant to other therapies. CDEC acknowledged that patients and clinicians highlighted the importance of having alternative treatment options for these patients. However, no direct evidence comparing etrasimod to other therapies was submitted.
- Results from the sponsor's network meta-analysis suggested that there [redacted].

- The oral route of administration of etrasimod may be more convenient for patients than many other therapies for UC that are administered through IV infusion or subcutaneous injection (i.e., biologics).

Background

UC is a chronic form of inflammatory bowel disease (IBD) that affects the mucosal layer of the large intestine and almost invariably involves the rectum and frequently extends continuously into the proximal colon. UC is characterized by blood in the stool with mucus, frequent diarrhea, loss of appetite, and tenesmus (severe rectal cramps or spasms). Extraintestinal manifestations may also occur, such as arthritis. About 10% to 15% of patients with UC experience an aggressive course. Relapse is common, with the cumulative risk of relapse being 70% to 80% at 10 years. UC has a considerable impact on patients' HRQoL, their ability to perform their regular daily routines such as jobs or domestic chores, their caregivers and family, their workplace, and their community. Although the risk of mortality from UC itself is low, the disease is associated with increased risk of other complications (e.g., respiratory diseases, colorectal cancer, lymphoma, and skin cancer) that result in higher mortality compared to the general population. The prevalence for UC in 2023 was estimated to be 414 per 100,000 in Canada. It is estimated that that 32% to 46% of people in Canada with UC have moderate disease and 13% to 14% have severe disease.

The clinical expert consulted for this review pointed out that treatment goals for patients with UC are to achieve rapid, symptomatic relief and to induce and maintain clinical, serological, biomarker, and endoscopic remission in both the short and long term. In patients with moderately to severely active UC, oral corticosteroids are typically the first-line therapy, but only used for inducing remission because of their adverse effects. Thiopurines (e.g., azathioprine, 6-mercaptopurine), 5-aminosalicylic acid (5-ASA), anti–tumour necrosis factor therapy, or vedolizumab can be used to maintain remission. For patients with disease for which 5-ASAs, corticosteroids, or thiopurines are unable to induce or maintain remission, or who cannot tolerate these drugs, advanced therapies are used. Of note, most Canadian drug plans require a patient with moderately to severely active UC to have disease that failed steroid tapering with azathioprine or 6-mercaptopurine before being eligible for an advanced therapy. As such, advanced therapies are typically not used for first-line maintenance of steroid-induced remission. Under circumstances where medical therapy fails, colectomy (which is associated with risks of complications and additional procedures) may be required. The clinical expert consulted for this review noted that early introduction of effective advanced therapy is important for patients' benefit, particularly in avoiding the adverse effects of repeated courses of corticosteroids because of their multiple adverse effects, not ideal on a repeat basis for control of UC symptoms. The clinical expert consulted for this review and the sponsor indicated that there is limited robust evidence; thus, no recent guidelines from Canada guiding preferred sequencing (that is, which drug is optimally use first) for advanced therapies in UC.

Etrasimod is a selective sphingosine 1-phosphate receptor modulator approved by Health Canada for the treatment of adults with moderately to severely active UC whose disease has had an inadequate response or lost response, or who were intolerant, to either conventional therapy or an advanced treatment. Etrasimod is available as 2 mg oral tablets and the recommended dose is 2 mg taken once daily.

Sources of Information Used by the Committee

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

- a review of 2 randomized controlled trials in patients aged 16 to 80 years with moderately to severely active UC and 1 indirect treatment comparison
- patients' perspectives gathered by 2 patient groups, the Gastrointestinal (GI) Society and Crohn's and Colitis Canada (CCC)
- input from the public drug plans that participate in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with UC
- input from 1 clinician group, the Canadian IBD Interest Group
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups that responded to CADTH's call for input and from a clinical expert consulted by the review team for the purpose of this review.

Patient Input

Two patient groups, the GI Society and CCC, provided input for this review. The GI Society's input was informed by surveys conducted between 2015 and 2023 (N = 54 to 579), focus groups, and 1-to-1 interviews with patients with IBD. CCC's input was compiled from 2 online surveys conducted in 2022 (by 354 patients with moderate to severe UC and 4 patients with UC, respectively).

From the patients' perspective, UC has a profound effect on daily life — physically, emotionally, and socially — at home, school, or in the workplace. Symptoms can be relentless, embarrassing, and scary. Sustained remission and/or treatment response is important. The concern of future flares, possibly worse than the last, at unpredictable times, remains constant among patients with UC. Patients noted that the most important aspects around UC management include having enough treatment options, treatments being well tolerated, and minimizing steroid use.

Clinician Input

Input From the Clinical Expert Consulted by the Review Team

The clinical expert noted that a significant portion of patients do not respond to available advanced therapies, and some become refractory over time. The clinical expert indicated that multiple drug failures and ongoing progressive disease activity may lead to adverse consequences, including surgery to remove the entire colon. Moreover, there is a lack of available oral therapies, as most are delivered intravenously or subcutaneously.

The clinical expert indicated that a clear sequence of medications that is optimal to treat moderate to severe UC is not yet established. The clinical expert noted that in an outpatient context, etrasimod could be introduced early, in the course of 5-ASA failure as it may induce remission, thus would not be reserved for patients for whom there are other contraindicated drugs, or other access limitations. The clinical expert noted that the evidence suggests the efficacy of etrasimod diminishes with more drug failures. Therefore, the clinical expert suggested that to optimize efficacy, etrasimod should be considered and administered to patients with UC earlier in their disease course.

The clinical expert noted that patients with a confirmed pathologic or histologic diagnosis of moderate to severe UC are typically diagnosed by a gastroenterologist and sometimes, in more rural parts of the country, a surgeon. Misdiagnosis is infrequent. The clinical expert noted that, although some clinical risk factors, such as early age of onset (under 40 years old), extensive colitis, and need for corticosteroids at diagnosis, may be associated with a more complex course, there are no currently available predictors of disease response to a therapy (e.g., generic profile or available blood tests).

The clinical expert outlined the most important patients outcomes at various stages as follows: first, in the short term, clinical response is important to ensure patients symptoms are manageable, including severe stool frequency, diarrhea, bleeding rectally, tenesmus, nighttime stooling, and urgency. Next, the intermediate-term main target is improvement in combination of symptom improvement and remission and resolution of both blood-based (C-reactive protein) and stool-based biomarkers (fecal calprotectin). Finally, usually within 6 months, the goal is ideally to exhibit endoscopic healing, or at least have significant improvement. The clinical expert indicated that for UC, the goal of exhibiting histologic healing is not currently considered a robust accepted treatment target, although there is evidence to suggest histologic healing does predict improved outcomes. Histologic healing is not used, however, as a clinical target in routine clinical practice. The clinical expert also noted that etrasimod would not likely be used in the acute, hospitalized setting for acute severe UC as this is a unique context with IV anti–tumour necrosis factor alpha drugs predominantly used as standard of care. The clinical expert noted that after the initiation of medication, a check-in within the first 1 to 2 weeks is essential to ensure some clinical improvement. Another check-in around 4 to 6 weeks is appropriate, followed by a full assessment with blood work and stool studies completed at 12 weeks. An endoscopic exam is preferred between 6 and 12 months of treatment initiation. The clinical expert indicated that treatment discontinuation of etrasimod should be considered in a similar manner to other advanced therapies for adults with moderate to severe UC, with factors including inability to decrease the oral corticosteroid dose despite treatment with etrasimod (steroid dependence); early recurrence of symptoms despite the full 12 weeks of initial therapy with etrasimod; persistent elevation of biomarkers, especially fecal calprotectin, and limited or no improvement of symptoms after 12 weeks of initial treatment with etrasimod; and evidence of persistent disease activity after initial therapy (12 weeks) or signs of progression during maintenance therapy based on endoscopy. The clinical expert noted that prescription of etrasimod should be limited to gastroenterologists who treat IBD, with the exception of internal medicine physicians or surgeons in rural settings.

Clinician Group Input

One clinician group that provided input was the Canadian IBD Interest Group, which is an assembly of gastroenterologists from across Canada with subspecialty expertise in IBD management. Their input was informed by 12 specialists.

In general, the input from the clinician group is in alignment with the clinical expert consulted for this review. The clinician group noted that treatment for UC is influenced by disease severity and may involve medications including oral and/or rectal 5-ASAs, systemic corticosteroids, advanced biologics (i.e., adalimumab, infliximab, golimumab, vedolizumab, ustekinumab, or mirikizumab) and advanced small molecule drugs (i.e., tofacitinib, upadacitinib, or ozanimod). The clinician group indicated that there a need for oral therapies that are well tolerated and provide durable disease control.

In alignment with the input from the clinical expert consulted for this review, the clinician group anticipated that etrasimod is likely to be used as a first-line advanced therapy and could also be used as a second- or third-line drug in selected cases for UC treatment, based on several advantages of etrasimod, including oral delivery; a once-daily dosing regimen; efficacy in all patient subgroups, including those with limited proctitis (the clinician group noted that patients with UC and ulcerative proctitis have been excluded from previous clinical trials but they represents up to 30% of the overall UC population); and a favourable long-term safety compared to existing oral alternatives, including ozanimod, upadacitinib, and tofacitinib. The clinician group noted that etrasimod would be unlikely to be used in patients with fulminant or hospitalized UC as this therapy has not been evaluated in that setting. The clinician group noted that discontinuation with etrasimod can be considered when there is an inadequate clinical response (assessment of both symptoms and objective biomarkers of disease activity) within 12 to 16 weeks of treatment, or a significant adverse effect occurs.

Drug Program Input

The clinical expert consulted for this review provided advice on the potential implementation issues raised by the drug programs (Table 2).

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
There are many conventional and advanced treatments in this space. Additionally, there is 1 other approved drug (ozanimod) that can be used as a comparator to etrasimod. The clinical trials compared etrasimod to placebo.	This is a comment from the drug plans to inform CDEC deliberations.
Considerations for initiation of therapy	
UC is diagnosed definitively through endoscopy. Other differentials can be ruled out through lab testing of blood or fecal matter testing for infectious causes. Scoring and/or staging:	This is a comment from the drug plans to inform CDEC deliberations. The clinical expert consulted for this review confirmed that UC is definitively diagnosed with endoscopically, through endoscopic assessment and histologic confirmation

Drug program implementation questions	Clinical expert response
• Mild: less than 4 stools per day, intermittent blood in stool, normal hemoglobin, ESR < 30, elevated CRP, Mayo subscore of 1 (via endoscopy) • Moderate to severe: > 6 stools per day, frequent blood in stool, hemoglobin < 75% of normal, ESR > 30, elevated CRP, Mayo subscore of 2 to 3 • Fulminant: > 10 stools per day, continuous blood in stool, requires blood transfusion, ESR > 30, elevated CRP, Mayo subscore 3 Etrasimod's indication is for moderate to severe UC. This is in line with comparator (ozanimod) and other advanced biologic and nonbiologic treatments.	(establishing chronicity). The clinical expert noted that the ESR is no longer used in UC diagnosis.
Ozanimod is approved for patients aged between 18 and 64 years. The sponsor of etrasimod is seeking funding for patients 18 years and older. Should etrasimod be approved for patients who are aged older than 64 years or be in line with ozanimod, noting the risk of bradycardia and/or reflex hypertension?	The clinical expert noted that patients of older age (e.g., aged over 64 years) are a more at-risk population because of comorbidities with the potential for multiple prescribed additional medications. Harms associated with S1P-receptor modulators like etrasimod include cardiac dysfunction, especially dysrhythmias. Currently, there is limited safety data in older patients with UC and even if these AEs turn out to occur infrequently, they could have important health consequences. Therefore, until there are more long-term harms data, clinicians would likely be cautious in starting etrasimod in older patients with UC and would prefer to prescribe other advanced therapies with well-established harms profile and the ones that clinicians have years of experience with (e.g., vedolizumab, ustekinumab, or mirikizumab). CDEC noted that a small proportion of patients enrolled in the ELEVATE UC 12 and ELEVATE UC 52 trials were aged ≥ 65 years (5.0% to 7.4% across the different groups); thus, there were limited safety data in this population of patients. Furthermore, CDEC acknowledged there may be additional safety concerns in older adults with comorbidities. CDEC noted that initiating etrasimod in patients who are aged 65 years and older should be based on clinician judgment after discussing with the patients.
The drug plans noted that 20% to 40% of patients receiving conventional therapy have disease that does not respond to treatment. Should patients require a trial of a conventional therapy (i.e., a 5-ASA, thiopurine, sulfasalazine, or corticosteroid) before initiation of etrasimod? Or should a diagnosis of moderate to severe UC give them access to etrasimod?	The clinical expert indicated that, based on evidence from the ELEVATE UC 12 and ELEVATE UC 52 trials, etrasimod would not be reserved for patients for whom there are other contraindicated drugs or other access limitations. The clinical expert noted the evidence suggests the efficacy of etrasimod diminishes with more drug failures. Therefore, to optimize efficacy, the clinical expert suggested that etrasimod be considered and administered to patients with UC earlier in their disease course (i.e., a trial of conventional therapy before initiation of moderate to severe UC would not be required). CDEC noted that the Health Canada indication and the pivotal trials' eligibility criteria required inadequate response to, loss of response to, or intolerance to at least 1 conventional or advanced therapy. Since first-line treatment is outside of the scope of the indication and CDEC did not review evidence in the

Drug program implementation questions	Clinical expert response
	first-line setting, CDEC could not recommend etrasimod as a first-line treatment for moderately to severely active UC.
Should patients who develop AEs such as transaminitis or lymphopenia be eligible for re-treatment once their lab values normalize?	The clinical expert pointed out that re-treatment would depend on the severity of abnormality in the patients' lab values (e.g., the level of liver enzyme to monitor the liver injury AEs), which may preclude the reintroduction of etrasimod.
Would patients with fulminant UC be eligible for treatment? Question to expert: Do you expect etrasimod to be used in CD?	The clinical expert pointed out that patients with fulminant UC would not be candidates for etrasimod. The clinical expert noted that etrasimod is unlikely to be used in patients with CD.
Ozanimod initiation criteria: mesalamine 4g per day for 4 weeks AND a corticosteroid (failure of disease to respond to prednisone 40 mg for 2 weeks or steroid dependent and unable to taper off) Proposed etrasimod criteria: failure of 5-ASA and/or corticosteroid There is a discrepancy in the proposed initiation criteria of etrasimod and the current criteria of ozanimod. The drug plans request that CDEC consider alignment with initiation criteria for ozanimod, if appropriate.	This is a comment from the drug plans to inform CDEC deliberations.
Considerations for continuation or renewal of therapy	
Reassessment is based on the Mayo score, which includes endoscopic findings. Will patients be required to have endoscopy done yearly to show remission? Or will a partial Mayo score suffice?	The clinical expert noted that patients should not be expected or required to undergo endoscopic examinations annually, and noted that there can be challenges with access to regular endoscopies. The clinical expert pointed out that surrogate measures, including the biomarker (level of fecal calprotectin), which is accurate in the detection of colonic inflammation, is used to determine the state of disease activity. The clinical expert noted that a partial Mayo score is also important in determining continuation or renewal of etrasimod. CDEC considered the invasive nature of an endoscopy and the limitations associated with timely access and associated costs of health care resources in Canada. CDEC considered it appropriate to leave the determination of clinical response up to the judgment of the treating physician who is experienced in the management of UC.
Ozanimod was recently negotiated with a successful LOI. The renewal criteria require reassessment by a specialist within 10 to 12 months and confirmation of a decrease in a partial Mayo score of greater than or equal to 2. Consider alignment with renewal criteria for ozanimod, if appropriate.	This is a comment from the drug plans to inform CDEC deliberations.
Considerations for discontinuation of therapy	
What parameters for discontinuation criteria should be considered? Should an increase in Mayo score be considered as discontinuation criteria?	The clinical expert indicated that the treatment discontinuation of etrasimod should be considered in a similar manner to other advanced therapies for adults with moderate to severe UC, with factors including: • inability to decrease the oral corticosteroid dose despite

Drug program implementation questions	Clinical expert response
	treatment with etrasimod (steroid dependence) • early recurrence of symptoms, despite the full 12 weeks of initial therapy with etrasimod • persistent elevation of biomarkers, especially fecal calprotectin, and limited or no improvement of symptoms after 12 weeks of initial treatment with etrasimod • evidence of persistent disease activity after initial therapy with etrasimod (12 weeks) or signs of progression during maintenance therapy based on endoscopy. The clinical expert noted that an increase in Mayo score alone is unlikely, but when it is used in combination with an increase in fecal calprotectin, they can be considered as discontinuation criteria for etrasimod.
Considerations for prescribing of therapy	
The drug plans noted that etrasimod is given once daily by mouth. Unlike ozanimod, etrasimod does not require induction and can be started at a therapeutic dose of 2 mg daily. The drug plans also noted that etrasimod is orally administered with no handling precautions.	This is a comment from the drug plans to inform CDEC deliberations.
There may be difficulties in access to gastroenterologists in rural settings. Virtual assessment could be an option. However, there is still the requirement for endoscopy to ensure diagnosis and potentially renewal criteria are met. Endoscopy may not be readily available to patients.	This is a comment from the drug plans to inform CDEC deliberations.
Will patients receiving etrasimod be eligible for additional treatment with biologics or JAK inhibitors? Criteria for ozanimod does not allow for additional treatment, but does allow for change in therapy to biologics or JAK inhibitors.	The clinical expert noted that it is not likely that etrasimod will be used in combination with other advanced treatments or JAK inhibitors. CDEC agreed there is no evidence to support the combination use of etrasimod with other advanced therapies for UC.
The drug plans asked for CDEC to consider alignment of prescribing criteria with ozanimod, as appropriate.	This is a comment from the drug plans to inform CDEC deliberations.
Care provision issues	
The drug plans noted that bradycardia, hypertension, transaminitis, and lymphopenia are expected adverse effects.	This is a comment from the drug plans to inform CDEC deliberations.
Should immunization be a requirement for prescribing etrasimod? If so, what vaccines (e.g., childhood vaccines, pneumonia, RSV, shingles)?	The clinical expert pointed out that it would be the safest to have immunization before prescribing etrasimod; however, mandating this is unlikely to be feasible.
The drug plans noted there is a need for initial assessment and monitoring — endoscopy, ECG to monitor QTc prolongation and evidence of second-degree AV block (should be readily available), fundoscopy in people with diabetes, and lab work for initial access and monitoring (LFTs, CBC). Question to clinical expert: Do you foresee access delays because of endoscopies? Do you expect issues with endoscopy being a criterion for renewal?	The clinical expert noted that the challenge in accessing endoscopic examination is universal across Canada for patients with UC (i.e., not unique to the administration of etrasimod). The clinical expert noted that the requirement of an endoscopic examination for etrasimod renewal would be prohibitive for use of etrasimod; and an endoscopic examination is not commonly applied to other UC medications' renewal, either. The clinical expert suggested that alternatively,

Drug program implementation questions	Clinical expert response
	a partial Mayo score could be used to determine etrasimod renewal.
System and economic issues	
There would be no concern if criteria and pricing is in line with recently negotiated ozanimod. The intention is for this to be an additional treatment tool for moderate to severe UC.	This is a comment from the drug plans to inform CDEC deliberations.
Ozanimod has recently completed negotiations and all jurisdictions participated on the LOI. Etrasimod would need confidential pricing equal to ozanimod as they are both in the same class of drug (S1P modulators).	This is a comment from the drug plans to inform CDEC deliberations.

5-ASA = 5-aminosalicylic acid; AE = adverse event; AV = atrioventricular; CBC = complete blood count; CD = Crohn disease; CDEC = Canadian Drug Expert Committee; CRP = C-reactive protein; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; JAK = Janus kinase; LFT = liver function test; LOI = letter of intent; QTc = corrected QT; RSV = respiratory syncytial virus; S1P = sphingosine 1-phosphates; UC = ulcerative colitis.

Clinical Evidence

Systematic Review

Description of Studies

Two multicenter, phase III, double-blind, randomized, placebo-controlled trials (ELEVATE UC 12 study, N = 354, and ELEVATE 52 study, N = 433) submitted by the sponsor were included that compared etrasimod (2 mg daily oral) with placebo in patients with moderately to severely active UC. In both trials, randomization was done by a 2:1 ratio and patients received either etrasimod or placebo for 12 weeks and 52 weeks, respectively. Clinical remission (defined as patients who had a stool frequence subscore of 0 [or 1 with a ≥ 1 point decrease from baseline], a rectal bleed subscore of 0, and an endoscopic score ≤ 1, excluding friability) was a primary outcome in both protocols. Key secondary outcomes were similar in both protocols, including endoscopic improvement, symptomatic remission, and mucosal healing. Corticosteroid-free clinical remission at week 52, and sustained clinical remission at both weeks 12 and 52, were also reported as the secondary outcomes in the ELEVATE UC 52 trial. HRQoL assessed with IBDQ was compared. Harms were also reported.

Patients in the trial populations had an approximate mean age of 40.5 years and a mean UC duration of 6.0 to 7.9 years. There were slightly more male (53% to 63%) than female (38% to 47%) patients. Most enrolled patients were white (75% to 89%), followed by Asian, Black or African American, American Indian or Alaska Native, and multiple. At baseline, approximately 27% to 32% of the patients were receiving a corticosteroid and 78% to 84% were receiving an oral 5-ASA. An approximate one-third of the patients enrolled reported prior use of at least 1 biologic or JAK inhibitor (29% to 34%).

Efficacy Results

The key efficacy results from the ELEVATE UC 12 and ELEVATE UC 52 trials are summarized in Table 3 in order of most important to less important outcomes, as suggested by the clinical expert consulted for this

review. According to the statistical analysis plans of both trials, the primary analysis of efficacy end points was conducted in the full analysis set (FAS) among patients with a baseline modified Mayo score of 5 to 9 (N = 334 in the ELEVATE UC 12 trial and N = 409 in the ELEVATE UC 52 trial).

Endoscopic Improvement

In both the ELEVATE UC 12 and ELEVATE UC 52 trials, a greater proportion of patients in the etrasimod group than in the placebo group had endoscopic improvement at week 12 and week 52. The between-group common risk differences were 12.1% (95% CI, 3.0% to 21.2%; P = 0.009) in the UC 12 trial and 21.2% (95% CI, 13.3% to 29.3%; P < 0.001) in the UC 52 trial at week 12, and 26.7% (95% CI, 19.0% to 34.4%; P < 0.001) in the UC 52 trial at week 52. Greater between-group risk differences were observed for patients treated with etrasimod versus placebo in the subgroup of patients who had not had experience with a prior biologic or JAK inhibitor therapy compared to those who had, and in the subgroup of patients who had received only 1, than those who received more than 1 prior biologic or JAK inhibitor (no interaction P values were provided).

Mucosal Healing

At week 52, a greater proportion of patients in the etrasimod group (26.6%) than in the placebo group (8.1%) had mucosal healing with a between-group common risk difference of 18.4% (95% CI, 11.4% to 25.4%; P < 0.001) in the ELEVATE UC 52 trial.

Clinical Remission

In both pivotal trials, a greater proportion of patients in the etrasimod group than in the placebo group had clinical remission at week 12 and week 52. The between-group common risk differences were 9.7% (95% CI, 1.1% to 18.2%; P = 0.026) in the ELEVATE UC 12 trial and 19.8% (95% CI, 12.9% to 26.6%; P < 0.001) in the ELEVATE UC 52 trial at week 12, and 25.4% (95% CI, 18.4% to 32.4%; P < 0.001) in the ELEVATE UC 52 trial at week 52.

Sustained Clinical Remission

A greater proportion of patients in the etrasimod group (17.9%) than in the placebo group (2.2%) had sustained clinical remission at week 12 and week 52, with a between-group common risk difference of 15.8% (95% CI, 10.7% to 21.0%; P < 0.001) based on the results from the ELEVATE UC 52 trial.

Corticosteroid-Free Clinical Remission

At week 52, a greater proportion of patients in the etrasimod group (32.1%) than in the placebo group (6.7%) achieved clinical remission and were corticosteroid-free for at least 12 weeks, with a common risk difference of 25.4% (95% CI, 18.4% to 32.4%; P < 0.001). Similarly, at week 52, among the patients who were receiving oral corticosteroids for UC at baseline, a greater proportion of patients in the etrasimod group (31.0%) than in the placebo group (7.5%) achieved clinical remission and were corticosteroid-free for at least 4 weeks, with a common risk difference of 23.1% (95% CI, 10.2% to 35.9%; P < 0.001).

Clinical Response

In both pivotal trials, a greater proportion of patients in the etrasimod group than in the placebo group had clinical response, with a between-group common risk difference of 21.2% (95% CI, 10.2% to 32.3%; P < 0.001)

in the ELEVATE UC 12 trial and 28.3% (95% CI, 18.5% to 38.0%; P < 0.001) in the ELEVATE UC 52 trial at week 12 and 24.9% (95% CI, 15.8% to 34.1%; P < 0.001) in the ELEVATE UC 52 trial at week 52.

Symptomatic Remission

At week 52, a greater proportion of patients in the etrasimod group (43.4%) than in the placebo group (18.5%) had mucosal healing, with a between-group common risk difference of 24.9% (95% CI, 16.2% to 33.6%; P < 0.001) in the ELEVATE UC 52 trial.

HRQoL Assessed With IBDQ Total Score

In the IBDQ total score of both pivotal trials, patients in the etrasimod group experienced a greater increase in mean change from baseline than those in the placebo group at week 12 and week 52. The least squares mean differences between the 2 groups were 17.33 points (95% CI, 8.50 to 26.16; P < 0.001) in the ELEVATE UC 12 trial and 15.44 points (95% CI, 6.54 to 24.35; P < 0.001) in the ELEVATE UC 52 trial at week 12, and 17.70 points (95% CI, 6.64 to 28.76; P = 0.002) in the ELEVATE UC 52 trial at week 52.

Harms Results

The analysis of harms was conducted in the FAS among patients with a baseline modified Mayo score of 4 to 9 (N = 354 in the ELEVATE UC 12 trial and N = 433 in the ELEVATE UC 52 trial). Evidence from the pivotal trials showed etrasimod was generally safe and well tolerated.

TEAEs were experienced by approximately 47% of patients in the ELEVATE UC 12 study and 56% to 71% of patients in the ELEVATE UC 52 study. The most common TEAEs in the 2 pivotal trials were anemia (6% to 10% across the different study groups), headache (2% to 8%), nausea (2% to 4%), UC (1% to 9%), and pyrexia (3% to 5%). In both trials, serious TEAEs occurred to approximately 2% to 7% of patients across the different treatment arms and were approximately similar between the 2 groups. The most frequently reported serious TEAEs and TEAEs leading to discontinuation of treatment in both trials was UC (not more than 2.5% across the study groups).

Across both trials, there was a greater proportion of patients in the etrasimod group who reported adverse events of special interest (AESIs) of cardiovascular events than in placebo group. Whereas there was a greater proportion of patients in the placebo group experiencing infections AESIs than those in the etrasimod. No AESIs of pulmonary disorders, macular edema, posterior reversible encephalopathy syndrome, progressive multifocal leukoencephalopathy, or malignancy were reported in the ELEVATE UC 12 study. Similar findings were demonstrated in the ELEVATE UC 52 study, except for 1 patient (0.3%) in the etrasimod group who reported macular edema and 1 patient in each treatment group (0.3% in the etrasimod group and 0.7% in the placebo group, respectively) who reported a pulmonary disorder.

Critical Appraisal

Both trials used appropriate randomization methods, allocation concealment, randomization stratification, double-blind approaches, and statistical methods for the primary and key secondary outcomes. Both trials used placebo as the comparator, and there is a lack of head-to-head, direct evidence comparing etrasimod against other active pharmacotherapies that are relevant to clinical practice in Canada. It is notable that the FDA guidance to industry for conducting interventional trials in patients with UC encourages sponsors to

use active treatments as controls. To align with the regulatory body's guidance on the moderate to severe UC population, which was available after or during the trials, the sponsor made the amendment in statistical analysis plans and performed the primary efficacy analysis in the FAS of patients with a baseline modified Mayo score of 5 to 9 (excluded a total of 44 patients with a baseline modified Mayo score of 4 in the 2 trials), although the overall trial population of patients who were randomized were those with a baseline modified Mayo score of 4 to 9. In general, the review team and the clinical expert consulted for this review did not identify major issues that would impact the study results with such a change in the efficacy analysis, based on the patient characteristics that appeared to be reasonably balanced between the treatment groups, and the similar findings in the supplementary analyses of the same outcomes using the entire FAS for both studies.

Some efficacy end points (e.g., modified Mayo score subscore of stool frequency and rectal bleeding and the HRQoL outcome assessed with IBDQ) were recorded and reported by patients. Although these subjective outcomes may be influenced by knowledge of treatment assignment, the double-blind design of the trials likely mitigated this risk. The review team noted that in the ELEVATE UC 52 trial, a higher proportion of patients in the placebo group discontinued the treatment because of worsening disease (50.7%) compared to those in the etrasimod group (27.3%) during the 52-week trial period. Withdrawal by patient as a reason for discontinuing the study or treatment was higher in the placebo group in both trials, except among those who discontinued the study in the ELEVATE UC 52 trial, in which a higher percentage of patients treated with etrasimod discontinued the study by patient choice. Also, for the IBDQ total score at week 52 in the ELEVATE UC 52 trial, the missing data rate was higher in the placebo group than in the etrasimod group. There was no concrete evidence beyond these points that clearly showed unblinding because of patients' inferences on treatment assignment based on symptom changes or other factors. Thus, the extent to which this could have affected efficacy and HRQoL outcome results, particularly the outcomes at week 52, is unclear. Overall, no important imbalances in baseline patient characteristics, concomitant medications, or dropouts of prognostic importance between the 2 study groups were identified. The overall concomitant use of systemic corticosteroids appeared similar between the groups in each study, although the reported use of budesonide by patients was 3% to 6% more in the etrasimod groups than in the placebo groups in both studies. As well, more patients treated with etrasimod (5.9% and 3.5%) than those treated with placebo (1.7% and 1.4%) concurrently received immunomodulators. While these are notable differences, the relatively small percentages (< 10%) and between-group differences (< 5%) means these were unlikely to have been important confounders of the trials' results. Overall, the statistical methods used in both trials were appropriate. The HRQoL assessed with IBDQ (other efficacy-related outcome) at week 52 was most likely underpowered as its outcomes data were only available for fewer than half of those with IBDQ assessed at baseline. The subgroup analyses were also likely underpowered to identify subgroup differences. An appropriate method for adjusting for multiplicity was used for the primary and secondary outcomes, but there was no multiplicity control for the subgroup analyses. The interaction P values for subgroup analyses were not provided.

While the indication for etrasimod is for the treatment of moderately to severely active UC in adults, patients aged 16 to 80 years were eligible for both trials, yet a relatively small proportion of the patients enrolled

(5.0% to 7.4%) were 65 years or older and 1 person was younger than 18 years in each study. There were no patients in the ELEVATE UC 12 trial and only 0.7% of the patients in the ELEVATE UC 52 trial who were 75 years or older at baseline. These small population results limit the trials' generalizability among the older patients. The clinical expert consulted for this review noted some caution when using etrasimod in patients who are aged 65 years and older because there is a higher likelihood of concomitant diseases and/or medications (polypharmacy), as well as the higher potential for decreased hepatic, renal, cardiac, or pulmonary function. Patients in both trials were recruited from multiple countries, including Canada. The clinical expert did not raise any major concerns in the generalizability of trials' results in clinical practice in Canada, based on the eligibility criteria of patients, the demographic characteristics of the patients from the diversity aspect, and the etrasimod dose in the 2 trials. The clinical expert pointed out that inclusion of patients with UC with isolated proctitis, a subgroup of patients with UC that is most often excluded from clinical trials, is helpful for clinical practice, contributing evidence for the efficacy and safety of etrasimod in this specific patient group. The clinical expert noted the importance of monitoring patients using biomarkers examinations (e.g., fecal calprotectin) during etrasimod treatment. The placebo-controlled period of the ELEVATE UC 52 trial was 1 year, which aligns with current regulatory guidance. However, given that patients and clinicians often report a waning of treatment effect with advanced therapies for UC, longer-term comparative evidence on the durability of etrasimod's effectiveness would be informative. The occurrence of some AEs, especially rarely ones, may take more than 52 weeks to be identified. Longer-term follow-up to assess safety and direct comparison between etrasimod to other advanced therapies would be preferred.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with the clinical expert, 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: endoscopic improvement, mucosal healing, clinical remission, sustained clinical remission, corticosteroid-free clinical remission, clinical response, symptomatic remission, change in IBDQ, and serious TEAEs.

Table 3 presents the GRADE summary of findings for etrasimod versus placebo in adults with moderately to severely active UC whose disease has had an inadequate response or lost response, or who were intolerant, to either conventional therapy or an advanced treatment.

Table 3: Summary of Findings for Etrasimod Versus Placebo for Adults With Moderately to Severely Active UC

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Endoscopic improvement				
Proportion of patients with endoscopic improvement Follow-up: 12 weeks	743 (2 RCTs)	ELEVATE UC 12 Trial • Etrasimod: 306 per 1,000 • Placebo: 188 per 1,000 • Difference: 121 more per 1,000 had	High[a]	Etrasimod results in a clinically important increase in the proportion of patients with endoscopic improvement

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		endoscopic improvement (95% CI, 30 to 212 more per 1,000) ELEVATE UC 52 Trial • Etrasimod: 350 per 1,000 • Placebo: 141 per 1,000 • Difference: 212 more per 1,000 had endoscopic improvement (95% CI, 130 to 293 more per 1,000)		at 12 weeks when compared to placebo.
Proportion of patients with endoscopic improvement Follow-up: 52 weeks	409 (1 RCT)	ELEVATE UC 52 Trial • Etrasimod: 372 per 1,000 • Placebo: 104 per 1,000 • Difference: 267 more per 1,000 had endoscopic improvement (95% CI, 190 to 344 more per 1,000)	High[a]	Etrasimod results in a clinically important increase in the proportion of patients with endoscopic improvement at 52 weeks when compared to placebo.
Mucosal healing				
Proportion of patients with mucosal healing Follow-up: 52 weeks	409 (1 RCT)	ELEVATE UC 52 Trial • Etrasimod: 266 per 1,000 • Placebo: 81 per 1,000 • Difference: 184 more per 1,000 had mucosal healing (95% CI, 114 to 254 more per 1,000)	High[b]	Etrasimod results in a clinically important increase in the proportion of patients with mucosal healing at 52 weeks when compared to placebo.
Clinical remission				
Proportion of patients with clinical remission Follow-up: 12 weeks	743 (2 RCTs)	ELEVATE UC 12 Trial • Etrasimod: 248 per 1,000 • Placebo: 152 per 1,000 • Difference: 97 more per 1,000 had clinical remission (95% CI, 11 to 182 more per 1,000) ELEVATE UC 52 Trial • Etrasimod: 270 per 1,000 • Placebo: 74 per 1,000 • Difference: 198 more per 1,000 had clinical remission (95% CI, 129 to 266 more per 1,000)	High[c]	Etrasimod results in a clinically important increase in the proportion of patients with clinical remission at 12 weeks when compared to placebo.
Proportion of patients with clinical remission Follow-up: 52 weeks	409 (1 RCT)	ELEVATE UC 52 Trial • Etrasimod: 321 per 1,000 • Placebo: 67 per 1,000 • Difference: 254 more per 1,000 had clinical remission (95% CI, 184 to 324 more per 1,000)	High[c]	Etrasimod results in a clinically important increase in the proportion of patients with clinical remission at 52 weeks when compared to placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Sustained clinical remission				
Proportion of patients with sustained clinical remission at both week 12 and week 52 Follow-up: 52 weeks	409 (1 RCT)	ELEVATE UC 52 Trial • Etrasimod: 179 per 1,000 • Placebo: 22 per 1,000 • Difference: 158 more per 1,000 had sustained clinical remission (95% CI, 107 to 210 more per 1,000)	High[d]	Etrasimod results in a clinically important increase in the proportion of patients with sustained clinical remission at both week 12 and week 52 when compared to placebo.
Corticosteroid-free clinical remission				
Proportion of patients with clinical remission at week 52 who were corticosteroid-free for ≥ 12 weeks Follow-up: 52 weeks	409 (1 RCT)	ELEVATE UC 52 Trial • Etrasimod: 321 per 1,000 • Placebo: 67 per 1,000 • Difference: 254 more per 1,000 had clinical remission and were corticosteroid-free for at least 12 weeks (95% CI, 184 to 324 more per 1,000)	High[e]	Etrasimod results in a clinically important increase in the proportion of patients with clinical remission at 52 weeks who were corticosteroid-free for at least 12 weeks when compared to placebo.
Proportion of patients (who were receiving oral corticosteroids for UC at baseline) with clinical remission at week 52 and were corticosteroid-free for ≥ 4 weeks Follow-up: 52 weeks	127 (1 RCT)	ELEVATE UC 52 Trial • Etrasimod: 310 per 1,000 • Placebo: 75 per 1,000 • Difference: 231 more per 1,000 had clinical remission and were corticosteroid-free for at least 4 weeks (95% CI, 102 to 359 more per 1,000)	High[f]	Etrasimod results in a clinically important increase in the proportion of patients (who were receiving oral corticosteroids for UC at baseline) with clinical remission at 52 weeks and were corticosteroid-free for at least 4 weeks when compared to placebo.
Clinical response				
Proportion of patients with clinical response Follow-up: 12 weeks	743 (2 RCTs)	ELEVATE UC 12 Trial • Etrasimod: 622 per 1,000 • Placebo: 411 per 1,000 • Difference: 212 more per 1,000 had clinical remission (95% CI, 102 to 323 more per 1,000) ELEVATE UC 52 Trial • Etrasimod: 624 per 1,000 • Placebo: 341 per 1,000 • Difference: 283 more per 1,000 had clinical remission (95% CI, 185 to 380 more per 1,000)	High[g]	Etrasimod results in a clinically important increase in the proportion of patients with clinical response at 12 weeks when compared to placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Proportion of patients with clinical response Follow-up: 52 weeks	409 (1 RCT)	ELEVATE UC 52 Trial • Etrasimod: 482 per 1,000 • Placebo: 230 per 1,000 • Difference: 249 more per 1,000 had clinical remission (95% CI, 158 to 341 more per 1,000)	High[g]	Etrasimod results in a clinically important increase in the proportion of patients with clinical response at 52 weeks when compared to placebo.
Symptomatic remission				
Proportion of patients with sustained symptomatic remission Follow-up: 52 weeks	409 (1 RCT)	ELEVATE UC 52 Trial • Etrasimod: 434 per 1,000 • Placebo: 185 per 1,000 • Difference: 249 more per 1,000 had symptomatic remission (95% CI, 162 to 336 more per 1,000)	High[h]	Etrasimod results in a clinically important increase in the proportion of patients with symptomatic remission at 52 weeks when compared to placebo.
HRQoL (IBDQ)				
Change from baseline in IBDQ total score (range of score, 32 [worst HRQoL] to 224 [best HRQoL]), LS mean change (SE) Follow-up: 12 weeks	592 (2 RCTs)	ELEVATE UC 12 Trial • Etrasimod: 47.49 points (SE = 2.87) • Placebo: 30.16 points (SE = 3.78) • Difference: 17.33 more points increase in IBDQ (95% CI, 8.50 points more to 26.16 points more) ELEVATE UC 52 Trial • Etrasimod: 42.79 points (SE = 2.77) • Placebo: 27.35 points (SE = 3.88) • Difference: 15.44 more points increase in IBDQ (95% CI, 6.54 points more to 24.35 points more)	Moderate[i]	Etrasimod likely results in little to no difference in IBDQ improvement at 12 weeks when compared to placebo.
Change from baseline in IBDQ total score (range of score, 32 [worst HRQoL] to 224 [best HRQoL]), LS mean change (SE) Follow-up: 52 weeks	168 (1 RCT)	ELEVATE UC 52 Trial • Etrasimod: 55.78 points (SE = 2.96) • Placebo: 38.08 points (SE = 4.95) • Difference: 17.70 more points increase in IBDQ (95% CI, 6.64 points more to 28.76 points more)	Low[j]	Etrasimod may result in little to no difference in IBDQ improvement at 52 weeks when compared to placebo.
Harms				
Proportion of patients with serious TEAEs Follow-up: 12 weeks	354 (1 RCT)	ELEVATE UC 12 Trial • Etrasimod: 25 per 1,000 • Placebo: 17 per 1,000 • Difference: NR	Moderate[k]	Etrasimod likely results in little to no difference in serious TEAEs at 12 weeks when compared to placebo.
Proportion of patients with serious TEAEs Follow-up: 52 weeks	433 (1 RCT)	ELEVATE UC 52 Trial • Etrasimod: 69 per 1,000	Moderate[k]	Etrasimod likely results in little to no difference in serious TEAEs at 52

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• Placebo: 63 per 1,000 • Difference: NR		weeks when compared to placebo.

CI = confidence interval; ES = endoscopic score; FAS = full analysis set; HRQoL = health-related quality of life; IBDQ = Inflammatory Bowel Disease Questionnaire; LS = least squares; MID = minimal important difference; MMS = modified Mayo score; NR = not reported; RB = rectal bleed; RCT = randomized controlled trial; SE = standard error; SF = stool frequency; TEAE = treatment-emergent adverse events; UC = ulcerative colitis.

Note: The primary analysis of efficacy end points was conducted in the FAS among patients with a baseline MMS of 5 to 9 (N = 334 in the ELEVATE UC 12 trial and N = 409 in the ELEVATE UC 52 trial). Study limitations (which refers 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 following footnotes.

[a]Endoscopic improvement was defined as patients with an ES of ≤ 1 (excluding friability). An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 5% between the groups was identified by the clinical expert consulted for this review as a threshold of clinical importance for this outcome. Although the lower boundary of the 95% CI for the between-group difference in the ELEVATE UC 12 trial was 3%, which could be considered as a source of serious imprecision, this did not result in the level of certainty of overall evidence for this outcome being rated down by also taking into consideration of evidence from the ELEVATE UC 52 trial.

[b]Mucosal healing was defined as patients who have an ES of ≤ 1 (excluding friability) with histologic remission measured by a Geboes Index score < 2.0. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 5% between the groups was identified by the clinical expert consulted for this review as a threshold of clinical importance for this outcome.

[c]Clinical remission was defined as patients who have an SF subscore of 0 (or 1 with a ≥ 1 point decrease from baseline), an RB subscore of 0, and an ES ≤ 1 (excluding friability). An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 7.5% between the groups was identified by the clinical expert consulted for this review as a threshold of clinical importance for this outcome. Although the lower boundary of the 95% CI for the between-group difference in the ELEVATE UC 12 trial was 1.14%, which could be considered as a source of serious imprecision, this did not result in the level of certainty of overall evidence for this outcome being rated down by also taking into consideration of evidence from the ELEVATE UC 52 trial.

[d]Sustained clinical remission was defined as patients with an SF subscore of 0 (or 1 with a ≥ 1-point decrease from baseline), an RB subscore of 0, and an ES of ≤ 1 (excluding friability) at both week 12 and week 52. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 10% between the groups was identified by the clinical expert consulted for this review as a threshold of clinical importance for this outcome.

[e]Corticosteroid-free for ≥ 12 weeks and achieved clinical remission at week 52 was defined as patients with an SF subscore of 0 (or 1 with a ≥ 1-point decrease from baseline), an RB subscore of 0, and an ES of ≤ 1 (excluding friability), who had not received corticosteroids for at least 12 weeks in the 40-week treatment period. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 7.5% between the groups was identified by the clinical expert consulted for this review as a threshold of clinical importance for this outcome.

[f]Corticosteroid-free for ≥ 4 weeks and achieved clinical remission at week 52 was defined as patients with an SF subscore of 0 (or 1 with a ≥ 1-point decrease from baseline), an RB subscore of 0, and an ES of ≤ 1 (excluding friability), who had not received corticosteroids for at least 4 weeks in the 40-week treatment period. The results of this outcome are among those who were receiving an oral corticosteroid for UC at baseline. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 7.5% between the groups was identified by the clinical expert consulted for this review as a threshold of clinical importance for this outcome.

[g]Clinical response was defined as patients with a ≥ 2-point and ≥ 30% decrease from baseline in MMS and a ≥ 1-point decrease from baseline in RB subscore or an absolute RB subscore ≤ 1. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 10% between the groups was identified by the clinical expert consulted for this review as a threshold of clinical importance for this outcome.

[h]Symptomatic remission was defined as patients with an SF subscore of 0 (or 1 with a ≥ 1 point decrease from baseline) and an RB subscore of 0. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 10% between the groups was identified by the clinical expert consulted for this review as a threshold of clinical importance for this outcome.

[i]The level of evidence was rated down by 1 level for serious imprecision. Based on the MID identified in the literature (≥ 15 points above placebo based on between-group data), the point estimate suggested little to no difference, and the 95% CI for the between-group difference crossed the MID threshold. The impact of missing outcomes data (less than 10% of the patients with the IBDQ results available at baseline in both the ELEVATE UC 12 and ELEVATE UC 52 trials, and no notable between-group imbalances in missing data were identified) is unclear.

[j]The level of evidence was rated down 1 level for serious risk of bias and was rated down 1 level for serious imprecision. More than half of the patients with the IBDQ results available at baseline had disease that did not respond at week 52, and there was a higher proportion of patients with missing data in placebo group than in the etrasimod group. No sensitivity analyses were done to assess the impact of the missing data for this outcome. While the exact impact of such missing outcomes data on the results is unclear, the review team considered that the risk of bias for this outcome was high. Based on the MID identified in the literature (≥ 15 points above placebo based on between-group data), the point estimate suggested little to no difference, and the 95% CI for the between-group difference crossed the MID threshold.

[k]The level of evidence was rated down 1 level for serious imprecision because of the small number of events.

Sources: ELEVATE UC 12 Clinical Study Report, ELEVATE UC 52 Clinical Study Report, and sponsor's submissions.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Information

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adults with moderately to severely active UC whose disease has had an inadequate response or lost response, or who were intolerant, to either conventional therapy (advanced therapy naive) or an advanced treatment[a] (advanced treatment experienced)
Treatment	Etrasimod
Dose regimen	2 mg once daily
Submitted price	$43.10 per 2 mg tablet
Submitted treatment cost	$15,688 per patient per year
Comparators[b]	• Adalimumab • Adalimumab biosimilar • Golimumab • Infliximab • Infliximab biosimilar • Mirikizumab • Ozanimod • Tofacitinib (branded) • Tofacitinib • Upadacitinib • Vedolizumab IV • Vedolizumab SC
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (60 years)
Key data source	Network meta-analyses; effectiveness of etrasimod informed by the ELEVATE UC 12 and ELEVATE UC 52 trials
Key limitations	• The comparative clinical efficacy of etrasimod relative to other advanced therapies is uncertain, owing to a lack of head-to-head trials and limitations with the sponsor's NMA. Indirect evidence submitted by the sponsor [redacted]. • The long-term effectiveness of etrasimod is highly uncertain owing to a lack of clinical data beyond 52 weeks. Although the sponsor incorporated the potential for treatment effectiveness waning, this was based on the results of the sponsor's NMA, which was associated with substantial uncertainty. In the sponsor's base case, 97% of the QALYs gained with etrasimod were accrued after 52 weeks on the basis of extrapolated data. • The modelling of subsequent therapy in the sponsor's model does not align with expected

Component	Description
	clinical practice and was informed by the results of the sponsor's NMA. Of the QALYs predicted by the sponsor's model to be gained with etrasimod, 88% to 90% were accrued after discontinuation of initial treatment (i.e., while patients were receiving subsequent therapy). • The sponsor's model did not adequately characterize decision uncertainty, as the efficacy inputs (i.e., clinical response, clinical remission) for the probabilistic model were hard coded based on iterations of the sponsor's NMA data. CADTH was unable to fully validate the sponsor's probabilistic model. • The impact of adverse events on costs and QALYs was not adequately considered, as only serious infections were included in the model. The product monograph for etrasimod includes a serious warnings and precautions note that includes malignancies, cardiovascular events, and liver injury; these were not considered in the sponsor's model. • The health state utility values adopted by the sponsor are markedly different from others in the published literature. Although these values have been used in prior submissions to CADTH, concerns regarding the reliability of these estimates were noted in all previous reviews. • The sponsor excluded infliximab and golimumab as comparators from the advanced therapy-experienced population, which was inappropriate according to the clinical expert input received by CADTH.
CADTH reanalysis results	• In the CADTH base case, CADTH adopted an equal probability for clinical response, remission, and serious infections for all advanced therapies and adopted alternate health state utility values. The price of tofacitinib was corrected to the generic price, in line with the amount reimbursed by public drug plans. • In the CADTH base case for both the advanced therapy-naive and advanced-therapy experienced subgroups, etrasimod was equally effective but more costly than the adalimumab biosimilar. There is insufficient clinical evidence to justify a price premium for etrasimod over currently available advanced therapies for moderately to severely active UC in either subgroup. To ensure cost-effectiveness, etrasimod should be priced no more than the lowest-cost advanced therapy used to treat moderately to severely UC that is funded.

LY = life-year; NMA = network meta-analysis; QALY = quality-adjusted life-year; SC = subcutaneous; UC = ulcerative colitis.

[a]The advanced therapies were assumed by the sponsor to include adalimumab (branded and biosimilar), golimumab, infliximab (branded and biosimilar), mirikizumab, ozanimod, tofacitinib (branded and generic), upadacitinib, and vedolizumab.

[b]The comparators included by the sponsor were the same for both subgroups, with the exception that golimumab and infliximab were excluded from the advanced therapy-experienced subgroup.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the market size and treatment costs were estimated using a claims-based approach, which introduces uncertainty that could not be resolved. Additional limitations included uncertainty in the market uptake of etrasimod, the market share of comparators, and the presence of confidential prices for most comparators.

The limitations of the claims-based approach to estimate the incremental budget impact could not be addressed by CADTH. Although the sponsor's base case estimates that the reimbursement of etrasimod will be associated with savings of $5,953,968 over 3 years (year 1 = $361,421; year 2 = $1,519,959; year 3 = $4,072,588), whether there will be cost savings and the extent of any savings realized by the drug plans is highly uncertain, and is likely to be affected by the market uptake of etrasimod and comparators, and the prices of advanced therapies for UC currently paid by the public drug plans.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, and Dr. Peter Zed

Meeting date: June 27, 2024

Regrets: One expert committee member did not attend.

Conflicts of interest: None

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