CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Ozanimod (Zeposia)

Indication: For the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, loss of response, or were intolerant to either conventional therapy or a biologic agent

Sponsor: Celgene Inc., a Bristol Myers Squibb Company

Recommendation: Reimburse with Conditions

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Single Technology

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that ozanimod be reimbursed for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

There is evidence from 1 phase III, randomized, double-blind, placebo-controlled trial that treatment with ozanimod results in added clinical benefit for adult patients with moderately to severely active UC. In the TRUE NORTH study (N = 645), greater percentages of patients in the ozanimod group compared with the placebo group had clinical remission during the induction period at week 10 (18.4% versus 6.0%; between-group difference of 12.4%; 95% confidence interval [CI], 7.5% to 17.2%; P < 0.0001) and maintenance period at week 52 (37.0% versus 18.5%; between-group difference of 18.6%; 95% CI, 10.8% to 26.4%; P < 0.0001). Similarly, there were statistically significant between-group differences in favour of the ozanimod group for clinical response, endoscopic improvement, and mucosal healing at weeks 10 and 52. During the maintenance period, there were statistically significant between-group differences in favour of the ozanimod group for corticosteroid-free remission, durable clinical remission, and maintenance of clinical remission. Patients indicated a need for new and effective treatment options to achieve sustained remission or response and symptom relief as patients may not have a response or may lose response to currently available treatment options. Ozanimod may address this unmet need as it is effective in inducing and maintaining clinical remission and has a different mechanism of action from currently available therapies for UC.

Results from a network meta-analysis (NMA) suggest that ozanimod may not be as efficacious in maintenance of clinical remission and response versus tofacitinib and vedolizumab and no more efficacious than other relevant advanced therapies (i.e., biologics and tofacitinib) for UC. Heterogeneity in terms of study design and patient characteristics across the included studies, insufficient analyses to account for heterogeneity, and inability to assess consistency between direct and indirect evidence contributed to uncertainty in the effect estimates.

Based on the submitted price for ozanimod and the publicly accessible list prices of all other advanced therapies, ozanimod was more costly than several relevant comparator treatments used in moderately to severely active UC. Given the uncertainty regarding the comparative clinical effectiveness and safety of ozanimod compared with other biologics and the limitations of the cost-utility analysis, there is insufficient evidence to justify a cost premium over the least expensive advanced therapy reimbursed for the treatment of moderately to severely active UC.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason	Implementation Guidance
Initiation		
1. The patient must be aged 18 and older with moderately to severely active UC and have had an inadequate response, had a loss of response, or been intolerant to conventional therapy or a biologic agent for UC.	Patients in the TRUE NORTH study were at least 18 years of age and had moderately to severely active UC while receiving conventional therapy. The study included both biologic-naïve and biologic-experienced patients. This aligns with the HC indication for ozanimod for UC.	—
2. The patient must have failed at least 1 biologic agent for UC.	In the TRUE NORTH study, ozanimod was not compared with a biologic agent for UC, which would have been the standard of care. Results from the sponsor-submitted ITC suggest that ozanimod may be less efficacious in clinical response and clinical remission during the maintenance phase than tofacitinib and vedolizumab and no more efficacious than other currently available advanced therapies for UC (i.e., biologics and tofacitinib).	—
Renewal		
3. The patient must have achieved clinical response to induction therapy after 10 weeks of treatment initiation to continue to maintenance therapy.	In the TRUE NORTH study, patients had to have a clinical response at the end of the induction period at week 10 to continue in the maintenance period.	The clinical expert indicated that an initial assessment should ideally be performed within 2 to 3 months after starting treatment. The Mayo score was used to determine clinical response in the TRUE NORTH study. However, CDEC considered the impracticality of requiring endoscopy within 12 weeks of treatment initiation given the invasive nature of the procedure and potential difficulties with timely access to the procedure. The clinical expert noted that sigmoidoscopy may be a useful tool for assessing patients if endoscopy is not feasible. Ultimately, CDEC considered it appropriate to leave the determination of clinical response up to the clinical judgement of the treating physician.
4. Assessment for renewal after the first assessment of treatment response should be performed every year. The patient must maintain clinical response to therapy to continue receiving ozanimod.	Patients who lose response to ozanimod are no longer benefiting from treatment.	—
Prescribing		

Reimbursement Condition	Reason	Implementation Guidance
5. Ozanimod should only be prescribed by a physician experienced in the diagnosis and management of UC.	It is important to ensure that ozanimod is only prescribed for appropriate patients.	—
6. Ozanimod should not be used in combination with other advanced therapies (biologics or Janus kinase inhibitors) for UC.	There is no evidence to support the use of ozanimod in combination with a biologic therapy or Janus kinase inhibitor for UC.	—
7. The dosage of ozanimod should not exceed 0.92 mg daily.	The clinical expert emphasized that it would not be appropriate to increase the dosage of ozanimod past the HC-recommended dosage due to the higher potential for off-target adverse effects with small molecule drugs such as ozanimod.	—
Pricing		
8. Ozanimod should be negotiated so that it does not exceed the drug program cost of treatment with the least costly advanced therapy reimbursed for the treatment of moderately to severely active UC.	There is insufficient evidence to justify a cost premium for ozanimod over the least expensive advanced therapy reimbursed for moderately to severely active UC.	—
Feasibility of Adoption		
9. The feasibility of adoption of ozanimod must be addressed	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).	—

QALY = quality-adjusted life year; HC = Health Canada; ICER = incremental cost-effectiveness ratio; UC = ulcerative colitis.

Discussion Points

- Ozanimod provides another treatment option with a different mechanism of action from other currently available therapies for UC.
- Although subgroup efficacy analyses in the TRUE NORTH study were not controlled for multiplicity and were not part of the sample size considerations, the results were in favour of ozanimod versus placebo for inducing and maintaining clinical remission and response in patients with prior use of anti–tumour necrosis factor (anti-TNF) therapy.
- Patients described numerous and substantial negative impacts of UC on quality of life as well as schooling and career. However, CDEC noted that no conclusions could be drawn on health-related quality of life (HRQoL) and productivity outcomes in the TRUE NORTH study due to lack of control for multiplicity and potential bias from missing data at later time points.
- The oral route of administration of ozanimod may be more convenient for patients than other advanced therapies for UC, which are predominantly administered through intravenous infusion or subcutaneous injection.

Background

Inflammatory bowel disease (IBD) is a term used to describe disorders that involve chronic inflammation of the digestive tract. There are two main types of IBD: Crohn's disease and UC. Crohn's disease is characterized by inflammation of the lining of the digestive tract, often involving the deep layers of the digestive tract. UC causes inflammation and ulcers in the digestive tract, affecting the

innermost lining of the large intestine (colon) and rectum. While both diseases are characterized by diarrhea, abdominal pain, rectal bleeding, and weight loss, UC is characterized by blood in the stool with mucus, frequent diarrhea, loss of appetite, and tenesmus (strong urge to use the bathroom without necessarily having a bowel movement). The estimated incidence rate for UC in Canada ranges from a low of 8.4 per 100,000 people in Alberta to a high of 21.4 per 100,000 people in Nova Scotia. There are an additional 15,000 individuals living with IBD in Canada that are not clearly classified as having Crohn's disease or UC.

Anti-inflammatory drugs are typically used as first-line therapy for mild to moderate UC and include 5-aminosalicylates (mesalamine, balsalazide, and olsalazine), sulfasalazine, and corticosteroids. For patients who do not have an adequate response on a 5-aminosalicylate or corticosteroid, conventional immunosuppressants such as azathioprine, mercaptopurine, and methotrexate are treatment options. However, conventional immunosuppressants are generally ineffective as induction therapy and have considerable toxicities. Biologic therapies are the mainstay treatment for patients with moderate to severe UC and are used for induction and maintenance when other treatments have been unsuccessful, or in those who cannot tolerate other treatments. There are 3 main classes of biologics used to treat UC: anti–tumour necrosis factor (anti-TNF) drugs (infliximab, adalimumab and golimumab), anti-integrin drugs (vedolizumab), and anti–interleukin 12/23 drugs (ustekinumab). Tofacitinib, a Janus kinase inhibitor, is a small molecule drug that is also considered an advanced therapy along with the biologics. According to the clinical expert, all of these drugs are effective and each has its own advantages and disadvantages with respect to safety, convenience, and efficacy. Patients who do not have a response to, lose response to, or are intolerant to 1 advanced therapy can move to a different advanced therapy, with consideration for the reason for treatment failure as an important determinant of the second-line agent.

Ozanimod has been approved by Health Canada for the treatment in adult patients with moderately to severely active UC who have had an inadequate response, loss of response, or were intolerant to either conventional therapy or a biologic agent. Ozanimod is a sphingosine 1-phosphate receptor modulator. It is available as 0.23 mg, 0.46 mg, and 0.92 mg oral capsules and the dosage recommended in the product monograph is 0.92 mg once daily.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- a review of 1 clinical trial in adult patients with moderate to severe UC
- a review of 2 indirect treatment comparisons
- a review of 1 extension study
- patient perspectives gathered by 2 patient groups: The Gastroenterological (GI) Society and Crohn's and Colitis Canada (CCC)
- input from public drug plans that participate in the CADTH review process
- input from 1 clinical specialist with expertise diagnosing and treating patients with UC
- 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 groups who responded to CADTH's call for patient input and from the clinical expert consulted by CADTH for the purpose of this review.

Patient Input

The patient input received for this review was provided by the GI Society and CCC. The input provided by the GI Society included over 1,500 respondents and was sourced from 4 online surveys (2015, 2018, and 2020) of respondents with IBD, including UC; and one-to-one conversations and phone/email/social media interactions. The input provided from the CCC consisted of over 3,900 respondents with IBD and was sourced from multiple sources, including multiple surveys (2017 to 2018 and 2021) and a phone interview. The CCC input included 8 respondents with experience with using ozanimod for UC; all accessed ozanimod via a clinical trial.

Respondents from both groups reported that UC has had a profound effect on all aspects of life - physically, emotionally, and socially – regardless of if they are at home, school or in the workplace. Symptoms associated with UC such as diarrhea, rectal bleeding, abdominal pain, bloating, cramping, anemia due to blood loss, frequent and urgent bowel movements, and fatigue not only affect day-to-day living, but also cause anxiety, stress. Respondents from both groups experienced constant concerns about future flare-ups, which can be disrupting. Respondents reported decreased quality of life during periods of active disease, with patients having a significant experience of symptoms and very frequent need for the bathroom. Even during periods of remission, respondents reported the need to stay close to a bathroom, which was stressful and limited their activities. Moreover, due to the perceived stigma of UC, many report hiding their disease from work colleagues, friends, and family. In extreme cases, based on patient input received from the CCC, thoughts of suicide were reported due to the inability to control and cope with the impacts of UC on personal and social lives, as well as consequences in their career or school. Based the patient input received from the GI Society, only 24% of respondents with IBD reported that the currently available medications are adequate to control their disease. Patient groups indicated that available treatments initially may have helped relieve some of the symptoms, but the treatments were unsuccessful in controlling their symptoms. Respondents reported that the need for new and effective treatment options to achieve disease remission, and reduce or eliminate the debilitating symptoms of UC. Moreover, respondents stressed that sustained remission and/or treatment response is more important than relieving any 1 symptom.

Clinician input

Input from clinical experts consulted by CADTH

The clinical expert consulted by CADTH detailed 4 unmet needs related to therapies for treatment of UC. First, while currently available therapies are effective, most patients with UC are unable to achieve complete endoscopic remission. As such, better UC therapies are needed to break through the “therapeutic ceiling” of current treatments. Second, it is unknown what the best treatment strategies are for patients with moderate to severe UC. Currently, there are no predictive tools of which patients will respond to which therapy. Third, there is still uncertainty about the ideal long-term therapeutic target and the overall benefits of targeting clinical, endoscopic, and/or histologic remission. Finally, access to coverage for UC treatments presents a major burden to both patients and provider. Many jurisdictions require patients with UC to fail conventional immunosuppressant before biologics are approved.

The clinical expert consulted by CADTH indicated that the novel mechanism of ozanimod would be a valuable addition to the treatment paradigm since the current therapies for moderate to severe UC are limited. According to the clinical expert, ozanimod may become a first-line advanced therapy among patients who have failed 5-aminosalicylate given its oral route of administration and efficacy in treating moderate UC. The clinical expert indicated that ozanimod may be considered among patients who have failed other biologic therapies, although the data for its effectiveness after anti–tumour necrosis factor (anti-TNF) failure is less promising.

Clinician group input

No clinician group input was received for this review.

Drug Program Input

Table 2: Responses to Questions from the Drug Programs

Implementation Issues	Advice from CADTH
Considerations for initiation of therapy	
Consider alignment with criteria for tofacitinib (oral, small molecule therapy).	CDEC considered this request in their deliberations.
Consideration for continuation or renewal of therapy	
Consider alignment with criteria for tofacitinib.	The CADTH reimbursement recommendation for tofacitinib for UC specifies that patients be assessed after 8 weeks of therapy and discontinued if clinical response has not been achieved. The clinical expert highlighted that some patients may not have a clinical response until after the first 8 weeks of treatment and noted the constraints on how frequently patients can be assessed.

Implementation Issues	Advice from CADTH
	CDEC considered this request in their deliberations and noted that assessment of clinical response during induction in the TRUE NORTH study occurred 10 weeks after treatment initiation as opposed to 8 weeks.
Consideration for discontinuation of therapy	
Consider alignment with criteria for tofacitinib	CDEC considered this request in their deliberations.
Consideration for prescribing of therapy	
The requested reimbursement criteria include use in patients who were intolerant to either conventional therapy or a biologic agent. Would clinicians prescribe ozanimod along with a TNF-alpha inhibitor?	According to the clinical expert, advanced therapies are typically prescribed as monotherapy and are prescribed sequentially. Combination therapy with another advanced UC treatment (i.e., biologic or JAK inhibitor) is the exception, and only occurs in very rare cases where patients fail all available treatments and require an off-label option. CDEC agreed with the clinical expert and considered it reasonable to restrict reimbursement such that ozanimod cannot be combined with another advanced therapy for UC (including biologics and JAK inhibitors).
Generalizability	
Generalizability of results is limited for a subset of patients as patients younger than 18 years and older than 75 years of age were not studied.	The clinical expert noted that there are other options that would be potentially better suited for patients over 75 years of age. There are several reasons why it would be rarer to use ozanimod in older patients. First, UC is less common in older patients. Second, vedolizumab or ustekinumab is typically used in this population given the favourable side effect profiles of these drugs. Finally, this population is much more likely to be on other drugs or have cardiac or ocular comorbidities that would potentially be considered as relative contraindications to ozanimod. CDEC agreed with the clinical expert and noted that Health Canada has not authorized ozanimod for maintenance treatment of UC in patients 65 years or older.
Care provision issues	
Bradycardia can occur after first dose; the product monograph does not suggest starting in hospital to monitor. This may present as a potential issue in care provision.	According to the clinical expert, bradycardia is a result of a dosing effect, and it is not necessary to initiate ozanimod in hospital. In prescribing the medication, the first week of dosing is escalating and addresses the bradycardia. In the trials, this first dose effect is generally very mild, and a baseline ECG to rule out significant cardiac conduction abnormalities would occur (for which ozanimod would be contraindicated). When used for the multiple sclerosis indication, hospitalization for the first dose is unnecessary. Also, a recent integrated safety analysis demonstrated that the risk of clinically significant cardiac adverse events from ozanimod is very low. CDEC agreed with the clinical expert that it would not be necessary to initiate ozanimod in hospital. CDEC also noted that it is important for providers to be aware of the contraindication and warnings concerning the use of ozanimod in patients with cardiac conduction abnormalities.

CDEC = Canadian Drug Expert Committee; ECG = electrocardiogram; JAK = Janus kinase; TNF = tumour necrosis factor; UC = ulcerative colitis.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Study

One sponsor-conducted study which met the CADTH review protocol criteria was included in this systematic review. The TRUE NORTH study was a phase III, multicenter, randomized, double-blind, placebo-controlled trial of oral ozanimod as induction and maintenance therapy for adult patients with moderate to severe UC. A total of 1012 patients were enrolled across 250 sites from 29 countries in North America (including 8 sites in Canada), Europe, Asia Pacific, South America and South Africa. The trial consisted of a 10-week induction period followed by a 42-week maintenance period. The induction period was composed of 2 cohorts: cohort 1, in which patients were randomized in a 2:1 ratio to receive either ozanimod 0.92 mg daily (N = 429) or matching placebo (N = 216) in a double-blind fashion; and cohort 2 (N = 367), in which patients received open-label ozanimod 0.92 mg once daily. Patients were evaluated for clinical response and remission at Week 10 of the induction period. Patients who had a clinical response to ozanimod at the end of the induction period proceeded to the maintenance period and were rerandomized in a 1:1 ratio to receive either ozanimod 0.92 mg daily (N = 230) or matching placebo (N = 227) in a double-blind fashion. Patients who were randomized to placebo in the induction period and had a clinical response at Week 10 continued to receive placebo in the maintenance period. The results presented here are for cohort 1 of the induction period and the rerandomized patients of the maintenance period.

The primary outcome of the study was clinical remission as measured by the 3-component Mayo score, which includes the following components: rectal bleeding, stool frequency, and endoscopy findings. Each component is rated from 0 to 3, yielding a total score of 0 to 9. The key secondary end points were controlled for multiplicity using a statistical testing hierarchy and each study period was considered an independent study. The primary end point and the following key secondary endpoints were assessed in both the induction and maintenance periods: clinical response, endoscopic improvement, and mucosal healing. Key secondary end points assessed only in the maintenance period were clinical remission in patients who were in remission at week 10, corticosteroid-free remission, and durable clinical remission. Other efficacy outcomes, which were not controlled for multiplicity, included health-related quality of life (HRQoL) outcomes, as assessed by the EQ-5D-5L and the 36-Item Short Form Health Survey (SF-36), and work productivity, as assessed by the work productivity and activity impairment questionnaire in UC (WPAI-UC).

Patients who completed the induction period and did not have a clinical response were invited to participate in an optional open-label extension (OLE) study. Patients who completed the maintenance period or those who experienced disease relapse during the maintenance period were also provided the opportunity to enter the OLE study.

Nearly 90% of the study patients were White, more than half were male, and the mean age was 42 years. The mean 3-component Mayo Score ranged from 6.6 (standard deviation [SD] = 1.15) to 6.7 (SD = 1.31) across treatment groups in both study periods. Disease severity as assessed by mucosal appearance at endoscopy was classified as severe in approximately 60% and 50% of patients in the induction period and maintenance period, respectively. All patients were previously treated with other UC medications. Excluding patients who received placebo during the maintenance period, patients in each treatment group at the start of the induction and maintenance period had received the following previous UC medications: corticosteroids (70% to 78%), oral aminosalicyclic acids (97% to 99%), immunomodulators (37% to 46%), azathioprine (30% to 38%), mercaptopurine (less than 10%), methotrexate (less than 6%), anti-TNF biologics (28% to 33%, aside from 44% in the open-label ozanimod group), and non-anti-TNF biologics (14% to 29%).

Efficacy Results

Clinical remission

Clinical remission was measured at week 10 and week 52 using a 7-day score algorithm and was defined as: rectal bleeding subscore (RBS) of 0, stool frequency subscore of 0 or 1 (and a decrease of at least 1 point from the baseline), and endoscopy subscore of 0 or 1 point without friability. The proportion of patients in clinical remission was significantly higher among patients in cohort 1 of the induction period who received ozanimod compared to those who received placebo (18.4% versus 6.0%; difference in proportions of 12.4%; 95% CI, 7.5% to 17.2%; $P < 0.0001$) at week 10 and among patients who continued to receive ozanimod in the maintenance period compared to those who were rerandomized to placebo (37.0% versus 18.5%; difference in proportions of 18.6%;

95% CI, 10.8% to 26.4%; P < 0.0001). Subgroup analyses according to prior use of anti-TNF therapy (yes versus no), disease severity (moderate versus severe), and disease extent (left-sided versus extensive) also showed favourable results for ozanimod in the induction period with greater treatment effect estimates for patients with no prior use of anti-TNF therapy, moderate UC, and left-sided disease.

Clinical response

Clinical response was measured using a 7-day score algorithm and was defined as: a reduction from baseline in the 3-component Mayo score of at least 2 points and at least 35%, and a reduction from baseline in the RBS of at least 1 point or an absolute RBS of 0 or 1. The proportion of patients with clinical response was significantly higher with ozanimod compared to placebo during both the induction period (47.8% versus 25.9%; difference in proportions of 21.9%; 95% CI, 14.4% to 29.3%; P < 0.0001) and the maintenance period (60.0% versus 41.0%; difference in proportions of 19.2%; 95% CI, 10.4% to 28.0%; P < 0.0001).

Durable clinical remission

The proportion of patients with durable clinical remission, defined as patients in clinical remission at week 10 and at week 52 in all patients who entered the maintenance period, was significantly greater in patients who remained on ozanimod compared to patients rerandomized to placebo (17.8%versus 9.7%; difference in proportions of 8.2%; 95% CI, 2.8% to 13.6%; P = 0.003).

Maintenance of clinical remission

The proportion of patients who maintained clinical remission at week 52 in a subset of patients who were in clinical remission at week 10 was greater among those remained on ozanimod compared to patients rerandomized to placebo in the maintenance period (51.9% versus 29.3%; difference in proportions of 23.9%; 95% CI, 9.1% to 38.6%; P = 0.0025).

Endoscopic improvement

Endoscopic improvement was defined as an endoscopy subscore of 0 or 1 without friability. A greater proportion of patients randomized to ozanimod had endoscopic improvement compared to patients randomized to placebo at week 10

(27.3% versus 11.6%; difference in proportions of 15.7%; 95% CI, 9.7% to 21.7%; P < 0.0001). At week 52, the proportion of patients with endoscopic improvement was greater in patients who continued on ozanimod compared to those rerandomized to placebo (45.7% versus 26.4%; difference in proportions of 19.4%; 95% CI, 11.0% to 27.7%, P < 0.001).

Mucosal healing

Mucosal healing was defined as an endoscopy subscore of 0 or 1 without friability and a Geboes index score of less than 2. A greater proportion of patients randomized to ozanimod had mucosal healing compared to patients randomized to placebo at week 10 of the induction period (12.6% versus 3.7%; difference in proportions of 8.9%; 95% CI, 4.9% to 12.9%; P < 0. 001). At week 52 of the maintenance period, the proportion of patients with mucosal healing was greater in patients who continued on ozanimod compared to those rerandomized to placebo (29.6% versus 14.1%; difference in proportions of 15.6%; 95% CI, 8.2% to 22.9%; P < 0.001).

Corticosteroid-free remission

The proportion of patients with corticosteroid-free remission at Week 52 (clinical remission while off corticosteroids for at least 12 weeks) was greater among patients who remained on ozanimod compared to those rerandomized to placebo (31.7% versus 16.7%; difference in proportions of 15.2%; 95% CI, 7.8% to 22.6%; P < 0.001).

Harms Results

Adverse events

During the induction period, at least 1 treatment emergent adverse event (TEAE) was reported by 40.1% and 38.0% of patients in the cohort 1 ozanimod and cohort 1 placebo group, respectively. Among patients rerandomized to placebo and those who continued on ozanimod during the Maintenance Period, 36.6% and 49.1% of patients reported at least 1 TEAE, respectively.

The TEAEs reported by at least 2% of patients in any treatment group during the Induction Period were: anemia, nasopharyngitis, headache, nausea, alanine aminotransferase increase, pyrexia, arthralgia, colitis ulcerative, and upper respiratory tract infection. Of these, anemia, nausea, and pyrexia were not reported by any patients during the maintenance period with the remaining TEAEs reported by similar proportion of patients as in the induction period. Apart from anemia, which was reported in 4.2% to 5.6% of patients, these TEAEs were reported in less than 4% of any treatment group. The following commonly reported TEAEs were exclusive to rerandomized patients in the maintenance period: gamma-glutamyl transferase increased (0.4% to 3.0%), oedema peripheral (2.6%), and herpes zoster (0.4% to 2.2%).

Serious adverse events

During the induction period, serious TEAEs were reported by 4.0% and 3.2% of patients in the cohort 1 ozanimod group and cohort 1 placebo group, respectively. The most common serious TEAE reported in the induction period was colitis ulcerative in both treatment groups (approximately 1.4%). Additional serious TEAEs reported in the cohort 1 ozanimod group were anemia (0.9%) and appendicitis (0.2%).

During the maintenance period, 7.9% of patients rerandomized to placebo and 5.2% of patients who continued ozanimod reported at least 1 serious TEAEs. Serious TEAEs reported in at least 2 patients in the rerandomized placebo group included colitis ulcerative (4% in the rerandomized placebo group and 0.4% in the ozanimod group) and complicated appendicitis (0.9% in the rerandomized placebo group).

Withdrawals due to adverse events

Withdrawal from the study due to TEAEs during the induction period was similar across the treatment groups at approximately 3%. The most common reason for withdrawal due to TEAEs was colitis ulcerative (cohort 1 ozanimod: 0.7% and cohort 1 placebo: 1.9%). Two (0.5%) patients in the Cohort 2 ozanimod group discontinued from the study due to bradycardia.

The percentage of patients who withdrew from the study due to TEAEs during the maintenance period was 2.6% among those rerandomized to placebo and 1.3% in patients who remained on ozanimod. Four (1.8%) patients in the group rerandomized to placebo withdrew from the study due to colitis ulcerative.

Mortality

During the study period, only one death was reported, which was recorded in the induction period cohort 2 ozanimod group.

Notable harms

Of the serious or opportunistic infections reported as AEs of special interest, the only one reported in at least 2 patients in any treatment group was herpes zoster (induction period cohort 1 ozanimod: 0.5%; induction period cohort 2 ozanimod: 0.3%; maintenance period ozanimod: 1.7%). Each of the following infections was reported in 1 patient over all treatment groups and periods: pyelonephritis, vestibular neuronitis, pneumonia influenza, respiratory syncytial virus test positive, urinary tract infection, clostridium difficile infection, complicated appendicitis, gastroenteritis norovirus, large intestine infection, measles, and yersinia infection.

Macular edema was reported by 1 patient in the induction period cohort 1 ozanimod group and cohort 2 ozanimod group each, and in the maintenance period ozanimod group.

During the induction period, only the cohort 1 and cohort 2 ozanimod groups reported hepatic effects (0.5% or less of the group), including alanine aminotransferase increased, hepatic enzyme increased, aspartate aminotransferase, liver function test increased, and transaminases increased. In the maintenance period, blood bilirubin increase was reported in 1 patient rerandomized to placebo. Among patients who remained on ozanimod, alanine aminotransferase increase and liver function test increase were each reported in 1 patient.

Lymphopenia was reported in 2 (0.9%) patients in the maintenance period ozanimod group.

Critical Appraisal

The TRUE NORTH trial was limited by differential dropout between treatment groups in the maintenance period, and a study design that resulted in an enriched patient population entering the maintenance period. Although approximately 90% of randomized patients completed the induction period, only approximately 50% had a clinical response and continued into the maintenance period. Selection into the maintenance period based on clinical response likely created an enriched patient population that was more likely to benefit from ozanimod treatment compared with the indicated population as a whole. According to the clinical expert consulted by CADTH, this is a common trial design used in UC programs, as it is challenging to keep non-responders in a long-term study. Furthermore, of those who continued into the maintenance period, the proportion of patients who completed the trial among patients rerandomized to received placebo and those who continued to receive ozanimod was 54.6% and 80%, respectively. A greater proportion of patients in the rerandomized placebo group discontinued the maintenance period following disease relapse to enter the OLE study compared to the ozanimod group (35.7% versus 14.8%). Although the direction of any bias is unclear, it is possible that the differential drop-out rate between the 2 treatment groups may have introduced attrition bias in favour of ozanimod.

Patients had the opportunity to enrol in the OLE study where they would receive open-label ozanimod. There was significant study discontinuation due to disease relapse and entry into the OLE (34% of patients rerandomized from ozanimod to placebo and 14% of patients rerandomized from ozanimod to ozanimod). Additionally, there may be a subset of patients who experience delayed response to induction therapy and they would not have been eligible to continue in the maintenance period. All of these factors contribute to the difficulty in assessing the generalizability of efficacy results.

Indirect Comparisons

Description of studies

Two indirect treatment comparison (ITC) studies were reviewed. The sponsor-submitted ITC was a systematic review and NMA comparing ozanimod to currently existing medications for the treatment of moderately to severely active UC. One NMA study including ozanimod, for patients with moderate to severe UC was included from the CADTH literature search.

In the sponsor-submitted ITC, ozanimod was compared to ustekinumab, infliximab, certolizumab, adalimumab, vedolizumab, tofacitinib, golimumab, filgotinib, etrasimod, filgotinib, etrasimod or the biosimilar versions of these therapies, and placebo. Phase II or III RCTs were included. Clinical response, clinical remission, endoscopic improvement and safety were evaluated. In the study be Lasa et al., ozanimod was compared to infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, tofacitinib, etrolizumab, upadacitinib, filgotinib, etrasimod, TD-1473 and placebo. Phase III RCTs were included in this report. In the Lasa report, clinical remission and endoscopic improvement were evaluated. Safety outcomes were examined in the 2 ITCs.

In the sponsor-submitted ITC, 22 RCTs were included in the analyses. Bayesian NMAs were performed using random-effect or fixed-effect models in all analyses. Due to the significant heterogeneity observed across the included trials, especially the study designs which are common in UC, adjustments were made to the data in older treat-through trials to more closely resemble modern re-randomized trials in the maintenance phase. Patients in the induction phase ranged in mean age from 34.1 to 44.8 years, and mean Mayo score of 8.0 to 9.1. The sponsor report noted differences between trials with respect to percent male (ranged from 42% to 100%), mean CRP level at baseline (ranged from 7 mg/L to 35.8 mg/L), years since UC diagnosis (ranged from 3.8 years to 14.6 years), extent of disease (left-sided [15% to 63%] versus extensive [6.6% to 80.8%] versus other [0 to 63.4%]), and use of concomitant steroids (ranged from 25% to 100%). In the maintenance phase, baseline characteristics were only reported for the re-randomized arms of rerandomized trials. Patients in maintenance phase trials were mostly similar in terms of age and sex. Mean Mayo score was similar for most trials. In the Lasa report, NMAs were conducted using the multivariate frequentist approach on 23 RCTs. The mean age of patients in the induction phase ranged from 34.4 to 43 years, and females comprised 33.7% to 45.5% of the study populations. Eleven trials required patients to be naïve to anti-TNF biologics at study entry. Among studies that allowed but did not require prior therapy with anti-TNF biologics, there was variation in the percent of patients who did have prior therapy with these agents (15% to 58%). Reporting of disease duration varied across studies but appear comparable among studies (mean 3.8 to 14.6 years). Of the 22 studies evaluating maintenance therapy, 10 were done using a treat-straight-through strategy and 12 followed a

randomized responders design. Patients in the maintenance phase ranged in mean age from 34.4 to 43 years, and females comprised 33.7% to 47.7% of the study populations.

Efficacy Results

Clinical response

In the sponsor's report, results from the NMA suggested that for the induction phase, in the overall population, no treatment was favoured when ozanimod was compared with other active treatments for clinical response. Similar results were found for the biologic-naïve patients. Among biologic-exposed patients, there was no evidence for a difference between ozanimod and other relevant active treatments, except that ozanimod was favored over adalimumab (odds ratio [OR] = 3.13, 95% credible interval [CrI], 1.42 to 7.31). For the maintenance phase, in the overall population, results of the NMA showed no evidence for a difference between ozanimod and other active treatments, except that ozanimod had less favourable clinical response compared with vedolizumab 300 mg every 8 weeks (OR = 0.55, 95% CrI, 0.34 to 0.92), tofacitinib 5 mg (OR = 0.57, 95% CrI, 0.33 to 0.97), and tofacitinib 10 mg (OR = 0.40, 95% CrI, 0.23 to 0.69). Similar results were found for the biologic-naïve population. For biologic-exposed patients, there was no evidence for a difference between ozanimod and any of the active comparators.

Clinical remission

In the sponsor's report, for the outcome of clinical remission, for the induction phase, no treatment was favored when ozanimod was compared with other active treatments in the overall population. Similar results were found for the biologic-naïve patients. Among biologic-exposed patients, there was no evidence for a difference between ozanimod and other active treatments, except that ozanimod was favored over adalimumab (OR = 4.19, 95% CrI, 1.56 to 11.49). For the maintenance phase, there was no evidence for a difference between ozanimod and other active treatments, except that ozanimod had less favourable clinical remission compared to vedolizumab 300 mg every 8 weeks (OR = 0.56, 95% CrI, 0.34 to 0.92), tofacitinib 5 mg (OR = 0.57, 95% CrI, 0.34 to 0.97), and tofacitinib 10 mg (OR = 0.40, 95% CrI, 0.24 to 0.69). Similar results were found for the biologic-naïve population. For biologic-exposed patients, there was no evidence for a difference between ozanimod and any of the active comparators. In the Lasa report, no treatment was favored when ozanimod was compared with other active treatments for induction of clinical remission in the overall population, biologic-naïve patients, and biologic-exposed patients for induction of clinical remission.

Endoscopic improvement

In the sponsor's report, for the outcome of endoscopic improvement, for the induction phase, the NMA results found that there was no evidence for a difference between ozanimod and other active comparators, except that ozanimod was favored over adalimumab (OR = 2.04, 95% CrI, 1.16 to 3.76) in the overall population and in biologic-naïve patients (OR = 2.04, 95% CrI, 1.16 to 3.76). Among biologic-exposed patients, no active treatments were favored over others for endoscopic improvement. For the maintenance phase, there was no evidence for a difference between ozanimod and other active comparators, except that ozanimod had less favourable endoscopic improvement compared to vedolizumab 300 mg every 4 weeks (OR = 0.46, 95% CrI, 0.24 to 0.88) and tofacitinib 10 mg (OR = 0.42, 95% CrI, 0.22 to 0.79). For the biologic-naïve population, ozanimod had less favourable endoscopic improvement compared to tofacitinib 10 mg (OR = 0.34, 95% CrI, 0.15 to 0.77). For biologic-exposed patients, there was no evidence for a difference between ozanimod and any of the active comparators. In the Lasa report, endoscopic improvement results of the ITC suggested that ozanimod was favored over adalimumab (OR = 1.79, 95% CI, 1.07 to 3.01) for the overall population and in biologic-naïve patients (OR = 2.07, 95% CI, 1.14 to 3.74). In biologic-exposed patients, no treatment was favored over another for induction of endoscopic improvement.

Harms Results

NMA results showed that there was no evidence for a difference between ozanimod and other relevant active treatments for the incidence of any AEs, SAEs and AEs leading to discontinuation, for both induction and maintenance phase. For incidence of serious infections at induction, there was no evidence for a difference between ozanimod and any of the active comparators, except that golimumab was favored over ozanimod (OR = 0.04, 95% CrI, 0 to 0.79). At maintenance, there was no evidence for a difference between ozanimod and other active treatments in the incidence of serious infections.

Critical Appraisal

A significant concern with the ITCs presented is that the studies included in the analyses were highly heterogeneous in terms of both study design and patient characteristics. One of the major concerns with design heterogeneity in UC trials is how trials transition from the induction to the maintenance phase. In the sponsor-submitted ITC, adjustments were made to the data in older threat-through trials to more closely resemble modern re-randomized trials in the maintenance phase, in order to alleviate the impact of heterogeneity in study design on result interpretation. Different approaches have been adopted to address this heterogeneity, for example, re-calculated data from treat-through studies to mimic a re-randomized trial or inclusion of re-randomized trials only. Results of this sensitivity analysis suggested that exclusion of the re-calculated treat-through data did not alter the results from the base case analyses.

Other significant heterogeneities can be found in definition of clinical outcomes, timing of study endpoint evaluation, subgroup definitions, and patients' baseline characteristics. In the sponsor's ITC, a number of trial and patient characteristics were considered as treatment effect modifiers. Despite various statistical techniques being employed to lessen the impact of potential clinical heterogeneity on the estimated treatment effect of ozanimod, there is still significant uncertainty in the ITC results. In the Lasa report, patients' baseline characteristics were not reported in detail; therefore, limited data are available to examine the treatment effect and safety of ozanimod in the study population, in particular in the subgroups of patients who were biologic-naïve and biologic-exposed. In addition, there was insufficient analysis conducted to account for trial and clinical heterogeneity, thus limiting the utility and the robustness of the results.

In both ITCs, safety data were sparse and only available for the overall population. In addition, due to the low event rate for some of the safety outcomes, such as AEs leading to discontinuation and serious infections, wider credible intervals are observed, and the results interpretation is challenging.

Other Relevant Evidence

Description of studies

The phase III OLE study was summarized to provide additional evidence regarding the long-term safety and efficacy of ozanimod for the treatment of patients with moderately or severely active UC at the time points beyond the TRUE NORTH parent study. The OLE study included patients who completed at least 10 weeks of the induction period without experiencing a clinical response or completed the maintenance period to week 52 or those who experienced disease relapse during the maintenance period of the TRUE NORTH trial. Of the [redacted] patients entering the OLE study from the TRUE NORTH trial, [redacted] were enrolled after completing the induction period, [redacted] entered after completing the maintenance period and [redacted] entered after discontinuing from the maintenance period.

Efficacy Results

The long-term efficacy of ozanimod as measured in the OLE study found that at Week 46, [redacted] patients in the total group were in clinical remission, [redacted] had a clinical response, [redacted] met criteria for endoscopic improvement, and [redacted] patients were in corticosteroid-free remission. However, by week 142, the treatment response rates decreased markedly. The results from the OLE study; however, were limited by the relatively small number of patients evaluated at each assessment point. Additionally, there was a high rate of treatment discontinuations ([redacted]) during the OLE study mostly due to lack of response, [redacted].

Harms Results

[redacted]

Critical Appraisal

The OLE was a single group study which did not include an active or placebo comparison group; without a comparison group it is not possible to know the true benefit of treatment and it is difficult to interpret results. [redacted]

[redacted] the open-label administration of the drug could introduce bias as knowledge of the treatment may lead patients and investigators to overestimate its potential benefits and harms. [redacted] Eligibility criteria of the OLE study specified that patients had to complete the induction or maintenance periods of the parent TRUE NORTH study, or discontinue the maintenance period due to disease relapse, which potentially allowed for selection bias. [redacted] Additionally, there was a high rate of treatment discontinuations ([redacted]) during the OLE study mostly due to lack of response, [redacted] The inclusion of patients with no initial response to ozanimod during the TRUE NORTH parent trial ([redacted]) is likely to underestimate the benefit observed during this extension study compared to the maintenance period of the parent study. [redacted]

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Decision-tree followed by a Markov cohort model
Target populations	Adult patients (≥ 18 years of age) with moderately to severely active ulcerative colitis with or without prior exposure to biologic[a] agents (i.e., biologic-experienced, or biologic-naïve).
Treatment	Ozanimod
Submitted drug price	Ozanimod, 0.23 mg: $68.4929 per capsule[b] Ozanimod, 0.46 mg: $68.4929 per capsule[b] Ozanimod, 0.92 mg: $68.4932 per capsule[c]
Treatment cost	At the sponsor's reported price of $68.49 per capsule (multiple strengths: 0.25 mg; 0.5 mg and 1 mg), the annual cost of ozanimod is $25,000.
Comparators[d]	• TNF inhibitors (adalimumab [brand and biosimilar], infliximab [brand and biosimilar], golimumab) • JAK inhibitor (tofacitinib) • IL-12/IL-13 blocker (ustekinumab) • α4β7 integrin inhibitor (vedolizumab [IV and SC]) • Conventional therapy (combination of aminosalicylates, corticosteroids, and immunomodulators)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs and LYs
Time horizon	Lifetime (58 years)
Key data source	The TRUENORTH (NCT02435992) trial informed treatment efficacy and safety for ozanimod vs. placebo; an unpublished sponsor commissioned NMA informed comparative treatment efficacy between ozanimod and biologic comparators.
Key limitations	• There is a high degree of uncertainty in the comparative clinical efficacy and safety of ozanimod and biologic comparators. The applicability of the indirect evidence is impacted by the heterogeneity in study design and patient populations across trials. • The model lacked transparency. The coding was inefficient as simple calculations were spread over multiple sheets. • Utility estimates for non-surgical health states used in the sponsor's base case lack reporting quality since the study is only available as an abstract. Though these have been used in submissions to CADTH, concerns regarding the reliability of these estimates were noted in all previous reviews. • The proportion of patients receiving an escalated dose in the economic model is not consistent with the dose-mix studied in the included clinical trials that informed the model's comparative efficacy data.

Component	Description
	• The distribution of CT for adjunctive use with biologics, as well as resource use relevant to disease management was not reflective of current clinical practice. • The model was based on a key assumption that treatment response (and loss of response) remained fixed throughout the maintenance phase and over the lifetime time horizon (58 years) based on data from clinical studies (52 weeks). • The model included a biologic therapy (ustekinumab) that is not currently reimbursed for this indication by the Canadian publicly funded health care payer.
CADTH reanalysis results	• CADTH performed reanalyses by applying the following changes: excluding ustekinumab as a comparator; assuming the clinical efficacy and safety of all biologic treatments to be equal; applying alternate utility values for non-surgical health states; assuming the proportion of patients receiving an escalated dose to be zero across biologic therapies; adjusting the proportion of patients receiving concomitant CT across biologic therapies to reflect Canadian clinical practice; and, aligning disease management resource use to published literature. • Results from the CADTH base case were similar to the sponsor's results, as ozanimod was not amongst the optimal treatments in the biologic-naïve or biologic-experienced populations. The probability that ozanimod is cost-effective at a willingness-to-pay threshold of $50,000 per QALY was 0% in both analyses. Price reductions of 73% and 66% would be necessary for ozanimod to be cost-effective at this threshold in biologic-naïve and biologic-experienced populations, respectively. • Scenario analyses where numerical differences in clinical efficacy and safety between biologic therapies were explored, as well as non-constant loss of response, led to results where ozanimod was strictly dominated.

[a]Biologic refers to anti-tumor necrosis factor therapies (infliximab, adalimumab, and golimumab), and small molecule drugs (tofacitinib, ustekinumab and vedolizumab).

[b]$479.45 per multiple strengths 7-unit starter pack, available for days 1-7 only.
[c]$1,917.81 per 28-unit pack.

[d]All comparators are included in the biologic-naïve and biologic-experienced population analyses.

UC = ulcerative colitis; TNF = tumor necrosis factor; JAK = Janus kinase; IL = Interleukin; IV = intravenous; SC = subcutaneous; CT = conventional therapy; QALY = quality-adjusted life-year; LY = life-year; NMA = network meta-analysis; CEF = Cost-effectiveness frontier; ICER = incremental cost-effectiveness ratio.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: inclusion of ustekinumab as a treatment option, although it is not currently reimbursed for this indication by the Canadian publicly funded health care payer; exclusion of costs associated with concomitant CT when co-administered with a primary biologic therapy; the projected market share of ozanimod in the biologic-experienced population is overly optimistic; uncertainty in the projected capture rates of ozanimod; and uncertainty in the projected candidate population that would be prescribed ozanimod. CADTH reanalysis involved excluding ustekinumab from the list of reimbursed treatment options; aligning the distribution of patients receiving concomitant CT across biologic therapies with the CUA reanalysis; and revising ozanimod's market share for the biologic-experienced population in years 2 and 3. The sponsor's results suggested that the reimbursement of ozanimod would lead to a budgetary impact of $11,823,925 over a 3-year time horizon. In the CADTH base case, the budget impact of reimbursing ozanimod is expected to be $13,066,443 in year 1, $27,131,379 in year 2, and $34,040,229 in year 3, with a three-year total of $74,238,052. If dose escalation is applied to 30% of patients on adalimumab, golimumab, infliximab, vedolizumab (IV) and tofacitinib during maintenance, the estimate budget impact decreases to $45,563,070.

Canadian Drug Expert Committee (CDEC) Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting Date: May 25, 2022

Regrets

One expert committee member did not attend.

Conflicts of Interest

None