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CADTH Reimbursement Recommendation

Upadacitinib (Rinvoq)

Indication: For the treatment of adult patients with moderately to severely active ulcerative colitis who have demonstrated prior treatment failure, i.e., an inadequate response to, loss of response to, or intolerance to at least 1 of conventional and/or biologic therapy.

Sponsor: AbbVie

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Rinvoq?

CADTH recommends that Rinvoq be reimbursed by public drug plans for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have demonstrated prior treatment failure (i.e., an inadequate response to, loss of response to, or intolerance to at least 1 of conventional therapy and/or biologic therapy), if certain conditions are met.

Which Patients Are Eligible for Coverage?

Rinvoq should be covered for a similar patient population and in a similar way to other drugs currently reimbursed by public drug plans for the treatment of moderately to severely active UC.

What Are the Conditions for Reimbursement?

Rinvoq should only be reimbursed if it is prescribed by a physician experienced in treating UC, the dosage does not exceed the product monograph's recommended dosage, and it is not used in combination with biologics for UC. It should not cost more than other biologics or targeted synthetic drugs covered by the public drug plans for the treatment of moderately to severely active UC.

Why Did CADTH Make This Recommendation?

- Evidence from 3 clinical trials demonstrated that patients were more likely to have disease remission after 8 weeks and after 60 weeks of treatment with Rinvoq than with placebo. Patients were also more likely to have healing of the lining of the large intestine with Rinvoq versus placebo.
- Rinvoq may meet some needs that are important to patients, as it is an additional treatment option that induces and maintains disease remission.
- Based on CADTH's assessment of the health economic evidence, Rinvoq does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Rinvoq compared with the least costly biologic or targeted synthetic drug (e.g., tofacitinib) for patients with UC.
- Based on public list prices, Rinvoq is estimated to cost the public drug plans approximately $2,636,982 over the next 3 years.

Summary

Additional Information

What Is UC?

UC is an inflammatory bowel disease that causes irritation, inflammation, and ulcers in the lining of the large intestine. Signs and symptoms include bloody stool, frequent diarrhea, abdominal pain, loss of appetite, and the strong urge to use the bathroom without necessarily having a bowel movement. There is no cure for UC and patients usually have symptoms on and off for life. It was estimated that in 2018, there were 120,000 Canadians living with UC.

Unmet Needs in UC

Patients may not have a response to or may lose response to currently available therapies for UC. More treatment options are needed to achieve and maintain disease remission.

How Much Does Rinvoq Cost?

Treatment with Rinvoq is expected to cost approximately $20,861 to $28,493 per patient for the first year, and $17,965 to $27,010 per patient per year thereafter.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that upadacitinib be reimbursed for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have demonstrated prior treatment failure (i.e., an inadequate response to, loss of response to, or intolerance to at least 1 of conventional therapy and/or biologic therapy), only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

There is evidence from 3 phase III, randomized, double-blind, placebo-controlled trials that treatment with upadacitinib results in added clinical benefit for adult patients with moderately to severely active UC. Patients in the U-ACCOMPLISH (N = 522) and U-ACHIEVE Induction (N = 474) studies were randomized to upadacitinib 45 mg once daily or placebo for 8 weeks of induction therapy, and patients in the U-ACHIEVE Maintenance study (N = 1,046) were assigned to upadacitinib 15 mg once daily, upadacitinib 30 mg once daily, or placebo for up to 52 weeks of maintenance therapy. During the induction periods, in the upadacitinib versus placebo groups, clinical remission was achieved at week 8 in 26.1% versus 4.8% (between-group difference of 21.6%, with a 95% confidence interval [CI] of 15.8% to 27.4%) in the U-ACHIEVE Induction study and 33.5% versus 4.1% (between-group difference of 29.0% [95% CI, 23.2% to 34.6%]) in the U-ACCOMPLISH study. In the U-ACHIEVE Maintenance study, clinical remission was achieved at week 52 in 42.3% in the upadacitinib 15 mg group (difference versus placebo of 30.7% [95% CI, 21.7% to 39.8%]) and 51.7% in the upadacitinib 30 mg group (difference versus placebo of 39.0% [95% CI, 29.7% to 48.2%]). In addition, there were statistically significant differences in favour of the upadacitinib groups versus placebo groups in each study for clinical response, symptom relief, endoscopic improvement, endoscopic remission, and mucosal healing.

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. Upadacitinib may address the unmet need for effective treatment options, particularly in patients who lose response to or experience intolerance to other treatments, as it is effective in inducing and maintaining clinical remission and symptom relief.

Based on the submitted price for upadacitinib and the publicly accessible list prices of all relevant comparators, upadacitinib 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 upadacitinib compared with biologics and tofacitinib in the sponsor-submitted network meta-analysis (NMA), and the lack of direct comparative evidence with an active treatment, there is insufficient evidence to justify a cost premium over the least expensive biologic or targeted synthetic drug reimbursed for the treatment of moderately to severely active UC.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Eligibility for reimbursement of upadacitinib should be based on the criteria used by each of the public drug plans for reimbursement of other drugs for the treatment of moderately to severely active UC (i.e., biologics and/or tofacitinib).	The results of the U-ACCOMPLISH and U-ACHIEVE studies demonstrate that upadacitinib is an effective treatment for UC. The indirect evidence is insufficient to definitively conclude that upadacitinib is superior or inferior to a relevant comparator (i.e., biologics or tofacitinib).	—
Renewal		
2. The patient must have achieved clinical response to induction therapy after 8 weeks of treatment to continue reimbursement of maintenance therapy.	In the U-ACCOMPLISH and U-ACHIEVE studies, patients had to have a clinical response at the end of the induction period at week 8 to continue in the maintenance period. While some patients in the trials achieved clinical response during an additional 8 weeks of induction, the extended induction period goes beyond the recommended dosage in the Health Canada–approved product monograph.	The Mayo score was used to determine clinical response in the pivotal studies. However, CDEC considered the impracticality of requiring endoscopy within about 8 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 fecal calprotectin level and sigmoidoscopy may be useful tools for assessing patients if endoscopy is not feasible. Ultimately, CDEC considered it appropriate to leave the determination of clinical response up to the clinical judgment of the treating physician.
3. 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 reimbursement of upadacitinib.	Patients who lose response to upadacitinib are no longer benefiting from treatment.	—
Prescribing		
4. Upadacitinib should only be prescribed by a physician experienced in the diagnosis and management of UC.	It is important to ensure that upadacitinib is only prescribed for appropriate patients.	—
5. Upadacitinib should not be reimbursed when used in combination with biologics for UC.	There is no evidence to support the use of upadacitinib in combination with a biologic therapy for UC.	—

Reimbursement condition	Reason	Implementation guidance
6. The dosage of upadacitinib should not exceed 45 mg daily during induction or 30 mg daily during maintenance. Induction with the 45 mg daily dosage should not continue beyond 8 weeks.	Given the safety concerns with JAK inhibitors and the lack of evidence beyond these doses, CDEC noted the importance of not exceeding the product monograph's recommended dosage.	—
Pricing		
7. Upadacitinib should be negotiated so that it does not exceed the drug program cost of treatment with the least costly relevant comparator (i.e., biologics or targeted synthetic drugs) reimbursed for the treatment of moderately to severely active UC.	There is insufficient evidence to justify a cost premium for upadacitinib over the least expensive relevant comparator reimbursed for moderately to severely active UC.	—

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

Discussion Points

- Results from the sponsor's NMA suggested that upadacitinib was favoured compared with other currently available treatment options for both induction and maintenance, and there were no results to suggest that other treatment options were favoured over upadacitinib for efficacy. However, there was much uncertainty in the effect estimates from the NMA due to sparse networks, heterogeneity in patient characteristics and trial characteristics, wide credible intervals, and lack of direct evidence between upadacitinib and other active treatments. The safety data were particularly sparse and likely confounded by UC being reported as an adverse event (AE). Therefore, conclusions could not be drawn from the NMA; with the lack of direct evidence versus an active comparator, there is insufficient evidence to show superiority of upadacitinib versus any relevant comparators in terms of efficacy or safety.
- Upadacitinib and tofacitinib are Janus kinase (JAK) inhibitors that are treatment options for UC. Tofacitinib has largely been moved to postbiologic use due to safety concerns. The product monograph for tofacitinib has serious boxed warnings for serious infections, malignancies, thrombosis, and major adverse cardiovascular events. The product monograph for upadacitinib has the same boxed warnings based on the drug class, and it is noted that some malignancies have been observed in patients treated with upadacitinib. Upadacitinib has potentially greater receptor selectivity than tofacitinib, and the clinical expert indicated that in theory upadacitinib should have an improved safety profile over pan-JAK inhibitors like tofacitinib. However, CDEC noted the lack of evidence to support a safety benefit with upadacitinib over tofacitinib. Long-term head-to-head trials with larger sample sizes are needed to assess the risk of rare events and those that take longer to develop in patients.

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

Background

UC is the most common form of inflammatory bowel disease (IBD). Depending on the extent and severity of the disease, patients with UC may present with diarrhea with or without blood and mucus, urgency or tenesmus, incontinence, constipation, colicky abdominal pain, fever, malaise, and weight loss. Regardless of severity, UC is also associated with high rates of fatigue and sleep difficulties. The disease has negative physical, emotional, and social impacts on patients. Aggressive disease course is experienced in 10% to 15% of patients. It was estimated that more than 120,000 Canadians were living with UC in 2018.

The selection of treatment regimens for UC is guided by disease severity and extent. While different drug classes are available for long-term management of moderately to severely active UC, biologic therapies are the mainstay of 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. At present, biologics include tumour necrosis factor (TNF) alpha antagonists (adalimumab, infliximab, and golimumab), anti-integrin agents (vedolizumab), and interleukin 12/23 antagonists (ustekinumab). Small molecule drugs, which include JAK inhibitors (tofacitinib) and the sphingosine 1-phosphate (S1P) receptor agonist ozanimod, are also used in patients with moderate to severe UC. Despite access to a variety of treatment options, not all patients respond to the available treatments and may become refractory to the current treatment regimens.

Upadacitinib is a selective JAK1 inhibitor approved by Health Canada for the treatment of adult patients with moderately to severely active UC who have demonstrated treatment failure (i.e., an inadequate response to, loss of response to, or intolerance to at least 1 of conventional therapy and/or biologic therapy). Upadacitinib is available as 15 mg, 30 mg, and 45 mg oral extended-release tablets. The recommended induction dose is 45 mg once daily for 8 weeks. The recommended dose for maintenance treatment is 15 mg once daily; 30 mg once daily may be appropriate for some patients, such as those with refractory, severe, or extensive disease. For patients aged 65 years and older, the only recommended maintenance dose is 15 mg once daily.

Sources of Information Used by the Committee

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

- a review of 3 randomized controlled trials (RCTs) in adult patients with moderate to severe UC
- patients' perspectives gathered by 2 patient groups: the Gastrointestinal (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
- input from 2 clinician groups: the IBD Centre of British Columbia (BC), and the Atlantic Specialist Group jointly with the University of Calgary IBD Unit
- 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

Two patient groups submitted input: the GI Society and CCC. The GI Society is a national charity committed to research, advocacy, educational activities for people with GI and liver conditions, working closely with health care professionals and governments at all levels to improve care and treatment. CCC is a national, volunteer-based health charity committed to finding cures for IBD and improving the lives of children and adults affected by these diseases through research, patient programs, fundraising, spreading information, advocacy, and awareness activities. The information provided in the GI Society submission was gathered through various questionnaires distributed among patients with IBD in 2015 (n = 423), 2018 (n = 432), 2020 (n = 724), and 2022 (ongoing), as well as 1-to-1 conversations with patients; a patient roundtable; recent phone, email, and social media interactions; and stories submitted from patients over time. CCC compiled data from 2 online surveys (including 354 patients with moderate to severe UC and 2 participants in the Rinvoq clinical trial) conducted in 2023 and 1 phone interview with a patient who participated in the Rinvoq clinical trial.

Patients with UC commonly experience symptoms such as fecal urgency, poor control of bowel function, rectal bleeding, and abdominal pain. Patients commonly described flares, which occur at unpredictable times, as causing extreme pain and fatigue, with a need to be always near a bathroom; however, symptoms may be present even during periods of remission. UC has a profound effect on patients' physical, emotional, and social lives at home, school, or in the workplace, and is particularly difficult for children and young adults since it affects their sense of self. Based on the CCC survey, patients' most frequently reported UC-related complications were mental stress (65%), joint inflammation and arthritis (51%), fissures and hemorrhoids (40%), anemia (33%), skin conditions (approximately 30%), and malnutrition and weight loss (approximately 30%). Other potential complications include bowel obstruction, intestinal fistulas, abscesses, stricture, liver conditions, and cancer. Patients said their social lives and relationships with partners have been negatively affected by their UC and that they felt isolated due to misunderstanding of their condition. About 72% of respondents said they had to constantly adjust their lifestyle and expectations due to UC; 2 in 5 patients said they changed their travel plans and 1 in 5 patients said they changed their career aspirations.

According to the GI Society submission, patients considered sustained remission and treatment response more important than relieving any 1 symptom. Despite the available treatment options, patients have

difficulty obtaining remission or symptom relief and there is a need for additional, new, effective treatments that achieve mucosal healing and reduce symptoms. Patients want adequate access to medications that work to reduce preventable suffering and unnecessary use of health care resources, and that allow patients to live full and productive lives. Finally, the GI Society stated that having a treatment with oral administration rather than infusion or injection would be helpful for many patients.

Clinician Input

Input From Clinical Experts Consulted by CADTH

According to the clinical expert, although various treatment options are available for patients with moderately to severely active UC, not all patients respond to them, and they may become refractory to current treatments. In addition, some of the current treatments are associated with many safety concerns. Some treatments have lower patient adherence due to the inconvenient route of administration.

The expert indicated that patients with moderately to severely active UC, either biologic-naive or biologic-exposed, are suitable for treatment with upadacitinib. The expert also stated that if the patients could access upadacitinib without the need to have failed conventional therapies, immunomodulators, or previously available biologics, then access to upadacitinib would potentially cause a shift in the current treatment paradigm.

The expert noted that in clinical practice, clinical response and remission are assessed using the partial Mayo score or components of the Mayo score, along with certain biomarkers. Clinicians usually schedule a colonoscopy 6 months to 9 months after starting treatment with biologics or small molecules to examine endoscopic healing.

The expert also stated that treatment with upadacitinib should be discontinued if there is a lack of clinical response to induction therapy, or if there is disease progression.

Clinician Group Input

Two clinician groups submitted input on upadacitinib: 3 clinicians on behalf of the IBD Centre of BC, and 12 gastroenterologists and a nurse practitioner on behalf of the Atlantic Specialist Group jointly with members from the University of Calgary IBD Unit.

The clinician group input was consistent with that from the clinical expert consulted by CADTH in terms of unmet needs, place in therapy, patient population, assessing response to treatment, discontinuing treatment, and prescribing conditions. The clinician groups emphasized that upadacitinib should not be used in patients with history of thrombosis or coronary artery disease. In terms of the place in therapy of upadacitinib in clinical practice, both clinician groups agreed that upadacitinib would be used in various circumstances for these patients, including as first-line therapy.

Drug Program Input

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

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Due to the absence of direct head-to-head studies of upadacitinib with other active therapies for UC (filgotinib, tofacitinib, ozanimod, vedolizumab, ustekinumab, adalimumab, golimumab, and infliximab), an NMA was undertaken to evaluate the relative clinical effectiveness of upadacitinib vs. other treatment options for UC. The NMA demonstrated that upadacitinib 45 mg displayed superior efficacy vs. all comparators irrespective of prior biologic treatment in the induction phase. In the maintenance phase, with the bio-exposed patients, upadacitinib 30 mg displayed superior efficacy vs. all comparators in the proportion of patients achieving clinical remission, clinical response, and endoscopic improvement whereas upadacitinib 15 mg was ranked among the highest. **Question:** Were there methodological limitations in the NMA that would lead to doubt about the validity of its findings?	CDEC noted the limitations identified in the CADTH Clinical Review report that led to considerable uncertainty in the results from the NMA. These included sparse networks, heterogeneity in patient characteristics and trial characteristics, and inadequate adjustment for the clinical heterogeneity (including baseline disease severity and treatment exposure). CDEC agreed with the CADTH assessment that conclusions cannot be drawn regarding the comparative efficacy and safety of upadacitinib vs. the comparators in the NMA.
Considerations for discontinuation of therapy	
The use of tofacitinib for patients with moderately to severely active UC has been reviewed by CADTH. The CDEC recommendation for tofacitinib for UC is to discontinue initial treatment if clinical response is not achieved after 8 weeks. Clinical response can be based on total or partial Mayo score, or clinical judgment of the prescribing gastroenterologists. **Question:** Should the same discontinuation criteria be applied to upadacitinib?	The clinical expert disagreed that upadacitinib therapy should be stopped if clinical response is not achieved after 8-week therapy. In the clinical trials, if the patients do not have adequate response to the first 8-week treatment, they are allowed an additional 8-week treatment with upadacitinib. In clinical practice, it is common that clinicians prescribe an additional 8 weeks of treatment to patients who do not respond well in the first 8 weeks. Some patients may benefit from this extended therapy. CDEC noted that the limited evidence in the induction trials suggests that some patients who do not have clinical response after 8 weeks of induction therapy go on to have clinical response following an additional 8 weeks of induction. However, CDEC also noted that the recommended dosage in the product monograph for induction is upadacitinib 45 mg once daily for 8 weeks and that extending the induction period to 16 weeks would fall outside the recommended dosage.
Care provision issues	
The sponsor provided the following statement in the submission: "Studies suggest that inhibition of JAK1 may be largely responsible for the efficacy of JAK inhibition in immune-mediated diseases whereas differences in safety of JAK inhibitors may be due to selectivity for specific JAK isoforms." Both tofacitinib and upadacitinib have Health Canada black box warnings for infection, malignancy, and thrombosis. Health Canada specifically states that the thrombosis warning is because these events have occurred in patients taking upadacitinib. **Question:** Are the pivotal studies (U-ACHIEVE Induction, U-ACCOMPLISH, and U-ACHIEVE Maintenance) submitted by	The clinical expert responded that the study duration (up to 1 year) of the pivotal studies was short. Therefore, the studies were not adequately designed to assess the long-term safety of upadacitinib. CDEC agreed with the clinical expert.

Implementation issues	Response
the sponsor for UC adequately designed to assess the safety of upadacitinib? These trials assessed the efficacy and safety of upadacitinib in the study population for up to 1 year.	
Do clinicians believe upadacitinib is safer than other JAK inhibitors, such as the pan-JAK inhibitor, tofacitinib?	The clinical expert indicated that given its unique mechanism of action (as a selective JAK inhibitor), in theory, upadacitinib should have a better safety profile compared to the pan-JAK inhibitors (i.e., tofacitinib). CDEC noted that there is no evidence that upadacitinib is safer than tofacitinib given the lack of head-to-head trials comparing them in patients with moderate to severe UC and the inability to draw conclusions based on the reviewed NMA.
System and economic issues	
There are currently 5 tofacitinib generics under review by Health Canada, which means that when the generics are available, tofacitinib's price will significantly drop for the typical UC maintenance dose (5 mg PO BID). The price of the lowest maintenance dose for upadacitinib (15 mg PO QD) is $18,000 per year for the treatment of UC. **Question:** Is there a reason a public plan should pay a significant price premium for upadacitinib vs. tofacitinib generics?	The clinical expert indicated that if clinical evidence supports improved safety with upadacitinib over tofacitinib generics, then it is beneficial for the drug plans to pay a price premium for improved safety. Although a drug with a better safety profile might be more expensive, it would save more health care resources in the long-term (e.g., the expense of hospitalizations from treatment-related complications). CDEC acknowledged the expert's input and noted that there is insufficient evidence to support a price premium for upadacitinib over tofacitinib generics when they become available.
In addition to the significantly reduced price for tofacitinib generics, there are negotiated confidential prices for the biosimilars of adalimumab and infliximab, which places their prices in the ballpark of tofacitinib generics. There is also a negotiated price for vedolizumab. **Question:** Is there any reason a public plan should pay a significant price premium for upadacitinib vs. biosimilars of other biologics, such as TNF alpha inhibitors?	The clinical expert noted that clinical trial data has suggested that treatment with JAK inhibitors improves patient outcomes faster compared to biologics. If patients can be steroid-free faster with upadacitinib vs. biologics, it may be worth paying a premium. However, there is a lack of head-to-head trials to directly compare upadacitinib with biologics and provide compelling evidence on its superiority. CDEC acknowledged the expert's input and noted that there is insufficient evidence to support a price premium for upadacitinib over biosimilars of biologics for UC.

BID = twice daily; CDEC = CADTH Canadian Drug Expert Committee; JAK = Janus kinase; NMA = network meta-analysis; PO = orally; QD = once daily; TNF = tumour necrosis factor; UC = ulcerative colitis.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

Three phase III RCTs (the U-ACHIEVE Induction study, N = 474; U-ACCOMPLISH study, N = 522; and U-ACHIEVE Maintenance study, N = 1,046) submitted by the sponsor were included in this systematic review. The objectives of all 3 studies were to evaluate the efficacy and safety of upadacitinib in patients with moderately to severely active UC. The studies enrolled adult patients with a diagnosis of moderate to severe UC who had an inadequate response, loss of response, or were intolerant to either conventional therapy

or biologic agents. In the induction trials (the U-ACHIEVE Induction and U-ACCOMPLISH studies), eligible patients were randomized to receive oral upadacitinib 45 mg once daily or matching placebo for 8 weeks in a double-blind manner. At the end of the 8 weeks, those who were deemed clinical responders were eligible to enter the maintenance study (U-ACHIEVE Maintenance study), while nonresponders were given open-label upadacitinib for an additional 8 weeks. Clinical response was defined as decrease from baseline in the adapted Mayo score equal to or greater than 2 points, and equal to or greater than 30% from baseline, plus a decrease in rectal bleeding score (RBS) equal to or greater than 1 or an absolute RBS equal to or less than 1. Patients who entered the maintenance study were rerandomized and treated with oral upadacitinib 15 mg or 30 mg once daily, or matching placebo for up to 52 weeks. The primary efficacy outcome of these 3 studies was the proportion of patients achieving or maintaining clinical remission according to the adapted Mayo score (defined as a stool frequency score [SFS] ≤ 1, RBS of 0, and endoscopic subscore ≤ 1).

In the 2 induction trials, about 60% of patients were male and about 40% were female; 65% to 71% were white and 28% to 31% were Asian. The mean age of patients enrolled in the induction trials was 42 years to 44 years. At baseline, 50% to 53% of patients had inadequate response, loss of response, or intolerance to biologic therapy, and 47% to 50% of patients had inadequate response, loss of response, or intolerance to conventional therapy. The majority of the patients had a mean adapted Mayo score less than or equal to 7. Corticosteroids were the most commonly prescribed prior UC medications. During the maintenance therapy, patients' baseline characteristics were generally comparable to those in the induction period.

Efficacy Results

During the induction period of the U-ACHIEVE study, clinical remission based on adapted Mayo score at week 8 was achieved in 26.1% of patients in the upadacitinib group and 4.8% of patients in the placebo group; between-group difference was 21.6% (95% CI, 15.8% to 27.4%). In the U-ACCOMPLISH study, clinical remission per adapted Mayo score was achieved in 33.5% of patients in the upadacitinib group and 4.1% of patients in the placebo group; between-group difference was 29.0% (95% CI, 23.2% to 34.7%). At the end of the maintenance period of the U-ACHIEVE study at week 52, clinical remission was maintained in 42.3% of patients in the upadacitinib 15 mg group, 51.7% of patients in the upadacitinib 30 mg group, and 12.1% of patients in the placebo group; between-group differences were 30.7% (95% CI, 21.7% to 39.8%) for upadacitinib 15 mg versus placebo and 39.0% (95% CI, 29.7% to 48.2%) for upadacitinib 30 mg versus placebo. The proportion of patients achieving clinical remission at week 8 or maintaining clinical remission at week 52 was the primary efficacy outcome in all 3 studies.

Similarly, the results for the proportion of patients achieving clinical response, endoscopic improvement or remission, histologic improvement, and mucosal healing favoured patients who were treated with upadacitinib compared to those treated with placebo, for both the induction and maintenance period. For maintenance therapy, the treatment effect for upadacitinib 15 mg versus placebo was smaller than it was for upadacitinib 30 mg versus placebo. The clinical expert consulted by CADTH indicated that all of these between-group differences were clinically meaningful. Results of subgroup analyses based on patients' baseline characteristics were consistent with those in the overall population. The results for other efficacy outcomes suggested that treatment with upadacitinib was associated with better symptom relief and

improved health-related quality of life (HRQoL) compared to placebo, during both induction and maintenance periods. The changes in HRQoL measured with the Inflammatory Bowel Disease Questionnaire (IBDQ) and Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) favoured the upadacitinib therapy. The impact of UC on work was evaluated between the upadacitinib group and the placebo group; however, this outcome was not adjusted for multiplicity and the results should be interpreted with caution. Treatment with upadacitinib may be associated with lower rates of hospitalization due to UC, for both induction and maintenance periods.

Harms Results

The proportion of patients experiencing at least 1 AE during induction was different between the 2 induction trials. In the U-ACHIEVE Induction study, at least 1 AE was reported by 56.4% and 61.9% of patients in the upadacitinib group and the placebo group, respectively. In the U-ACCOMPLISH study, at least 1 AE was reported by 52.9% and 39.5% of patients in the upadacitinib group and the placebo group, respectively. UC was more often reported in the placebo groups and was a major driver when the risk of AEs, serious AEs (SAEs), or withdrawals due to AEs (WDAEs) was high in the placebo group compared to the upadacitinib group. This may be explained by the AE of "ulcerative colitis" being the exacerbation of a patient's existing condition of UC. Patients who were treated with placebo may have been more likely to experience the AE of UC, due to the lack of efficacy from the treatment of placebo. During the maintenance period, AEs were reported in 75.2%, 75.3%, and 73.5% of patients in the upadacitinib 15 mg, upadacitinib 30 mg, and placebo groups, respectively.

In the induction period, there were no AEs of active tuberculosis, malignancy, adjudicated venous thromboembolic events (VTEs), or GI perforation reported in the upadacitinib groups. The incidence of opportunistic infection excluding tuberculosis and herpes zoster, herpes zoster, lymphopenia, and neutropenia were higher in the upadacitinib groups. At the end of the maintenance period, patients treated with up to 1 year of upadacitinib reported cases of herpes zoster, neutropenia, malignancy, hepatic disorder, lymphopenia, and VTEs. The numbers of events were low for malignancy and VTE at this time point. Longer-term data are needed to fully understand the long-term safety profile of upadacitinib in patients with UC.

Critical Appraisal

Internal Validity

In the maintenance period, the discontinuation rates were high and imbalanced across treatment arms. In cohort 1, 30.4%, 18.8%, and 63.8% of patients in the upadacitinib 15 mg arm, upadacitinib 30 mg arm, and placebo arm discontinued the study, respectively. "Other" was the main reason for study discontinuation, and the majority of patients in this category were noted to have discontinued due to "lack of efficacy" or "loss of response." These patients would have been considered nonresponders in the efficacy analyses. A bias is less likely to be introduced in this circumstance.

Prespecified subgroup analyses were performed to examine the consistency of the treatment effect observed for the primary efficacy end points. However, proper interpretation of all subgroups was not possible due to lack of sample size considerations for these subgroups. The subgroups were underpowered

to detect significant effect modification by subgroups of interest, such as inadequate response to previous biologics.

External Validity

According to the clinical expert consulted by CADTH, the population included in the pivotal studies was generally consistent with clinical practice. Based on the patients' baseline characteristics, the study populations reflect a typical Canadian population that would receive upadacitinib in practice.

The U-ACHIEVE Induction and U-ACCOMPLISH studies included 8 weeks of induction therapy. The clinical expert consulted for this review indicated that this was a sufficient time frame to determine short-term treatment effects with upadacitinib. The U-ACHIEVE Maintenance study was a 52-week study. The expert noted that 52 weeks would not be considered sufficient to observe long-term safety of this drug for rare events, such as malignancy.

The patient population in the maintenance period was likely enriched due to the study design. Approximately 72% of patients responded to the treatment after 8 weeks of induction therapy, and it should be noted that the interpretation of the maintenance period results differs between a rerandomized design and a treat-through study design.

Indirect Comparisons

The sponsor-submitted indirect treatment comparison (ITC) provided indirect evidence on the efficacy and safety of upadacitinib relative to other active treatments for moderately to severely active UC. The active comparators for upadacitinib included other JAK inhibitors (tofacitinib and filgotinib), TNF alpha antagonists (adalimumab, golimumab, and infliximab), anti-integrin drugs (vedolizumab), IL-12/23 antagonists (ustekinumab), and an S1P receptor agonist (ozanimod). Relevant RCTs were identified through a systematic literature search. Twenty-three RCTs were included in the NMA. Outcomes of clinical remission, clinical response, and endoscopic improvement were evaluated in bio-naive patients and bio-exposed patients. Harms outcomes were evaluated in the overall population. A Bayesian NMA approach was taken for data synthesis.

In addition, 3 published ITCs (Lasa et al. [2022], Bur et al. [2021], and Li et al. [2022]) were identified from CADTH's literature search. Limitations in these studies included concerns of substantial heterogeneity from different sources and insufficient description of the methods used to address and adjust these heterogeneities; the underlying transitivity assumption of the NMA not being upheld; and wide confidence intervals or credible intervals of the effect estimates, meaning that the magnitude of the effects is uncertain. The authors' conclusions were provided in the CADTH Clinical Review report; however, due to the aforementioned limitations, the results of these ITCs were not described in detail.

Efficacy Results

Based on the results of the sponsor-submitted ITC, for the induction phase, treatment with upadacitinib 45 mg may be associated with higher rates of clinical remission, clinical response, and endoscopic improvement compared to some of the active comparators. The estimates are associated with considerable

uncertainty due to the lack of direct evidence, the sparsity of the network, and the potential for the transitivity assumption to have been violated. Analysis of findings for the maintenance phase required adjustment for differences in study designs, and there were fundamental differences in the placebo arms across the studies. The statistical techniques adopted in the sponsor's ITC are possible strategies to address cross-study heterogeneity, lessen the impact of potential clinical heterogeneity on the estimated treatment effect of upadacitinib, and make NMAs feasible; however, they cannot adequately remove uncertainty to allow for firm conclusions. Therefore, firm conclusions could not be established for the efficacy of upadacitinib compared with other relevant active treatments in achieving clinical response, clinical remission, and endoscopic improvement.

Harms Results

Due to the limitations in the sponsor-submitted ITC, a conclusion regarding the safety of upadacitinib relative to other active treatments cannot be drawn.

Critical Appraisal

In the sponsor-submitted ITC, sources of heterogeneity and potential treatment effect modifiers (such as study design [e.g., inclusion and exclusion criteria, and outcome definitions] and notable heterogeneity in a number of patients' baseline characteristics [e.g., previous UC medications or differences across the placebo arms]) in the included studies were identified, and some were addressed in data analyses. However, in several studies, data for potential effect modifiers were unavailable. The maintenance phase in particular is problematic. Some of the placebo arms were considered fundamentally different from each other. Given these concerns, the transitivity assumption in an NMA may not be upheld. Despite various statistical techniques being employed to lessen the impact of potential clinical heterogeneity, such as baseline risks on the estimated treatment effect of upadacitinib, there is still uncertainty in the ITC results. The approaches used to adjust the differences in study design (treat-through versus rerandomization) are potential solutions to adjust the cross-study heterogeneity in UC trials; however, it is uncertain whether the adjustment is adequate. In addition, the network is sparse. Coherence could not be assessed due to the lack of relevant closed loops when comparing to other active treatments. All evidence is indirect, which reduces our certainty in the study findings. Wide credible intervals were observed for many efficacy and safety outcomes, especially in the maintenance phase. This implies considerable uncertainty in the magnitude of treatment effects of upadacitinib.

Safety data were sparse and only available in the overall population. These data are likely confounded by efficacy, since UC is commonly reported as an AE, SAE, and WDAE in clinical trials of UC.

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 population	Adult patients (≥ 18 years of age) with moderate to severe active UC with or without prior exposure to biologic[a] drugs (i.e., biologic-experienced or biologic-naive).
Treatment	Upadacitinib
Dose regimen	Treatment with upadacitinib is initiated with an 8-week induction period, during which patients receive a dose of 45 mg once daily. The recommended dose for maintenance treatment is 15 mg once daily. For some patients, such as those with refractory, severe, or extensive disease, a maintenance dose of 30 mg once daily may be appropriate.
Submitted price	Upadacitinib, 15 mg: $49.22 per tablet Upadacitinib, 30 mg: $74.00 per tablet Upadacitinib, 45 mg: $101.81 per tablet
Treatment cost	Assuming the lowest maintenance dose (15 mg), at the sponsor's reported price of $49.22, $74.00, and $101.81 per 15 mg, 30 mg, and 45 mg tablet, respectively, the annual cost of upadacitinib is $20,861 for year 1 and $17,965 thereafter. Assuming the highest maintenance dose (30 mg), at the same reported prices, the annual cost of upadacitinib is $28,493 for year 1 and $27,010 thereafter.
Comparators	• TNF inhibitors (adalimumab biosimilar, infliximab biosimilar, golimumab) • JAK inhibitor (tofacitinib) • Alpha-4 beta-7 integrin inhibitor (vedolizumab IV) • Conventional therapy (combination of aminosalicylates, corticosteroids, and immunomodulators)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (57 years)
Key data source	The phase III clinical program, comprised of 3 pivotal multicentre, double-blind, placebo-controlled studies, of which 2 are replicate induction studies (the U-ACHIEVE Induction and U-ACCOMPLISH studies) and 1 a maintenance study (the U-ACHIEVE Maintenance study). These informed the efficacy and safety of upadacitinib, while a sponsor-commissioned NMA informed the efficacy and safety of comparators, including CT.
Key limitations	• The comparative clinical efficacy and safety of upadacitinib vs. relevant comparators (i.e., biologics and tofacitinib) is highly uncertain. The applicability of the indirect evidence is impacted by the heterogeneity in study design and patient populations across trials included in the NMA. As a result, the efficacy of upadacitinib in comparison with relevant comparators is uncertain based on CADTH's appraisal of the sponsor's submitted NMA, regardless of the maintenance dose received. • AEs related to serious infections were assumed to occur only during the 8-week induction period; however, AEs are expected to occur beyond the first 8 weeks of treatment. The CADTH appraisal of the submitted NMA could not conclude any difference in the incidence of serious infections between upadacitinib and relevant comparators. The sponsor also omitted several key AEs associated with upadacitinib noted in the product monograph.

Component	Description
	• 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 (57 years) based on data from clinical studies (52 weeks) in the absence of long-term evidence. This assumption is highly uncertain. • Concomitant use of conventional therapy while on primary "advanced" therapy (i.e., upadacitinib, tofacitinib, or biologics) was absent from the analysis despite anticipated differences in the use of CT between the therapies. • Disease management resource utilization was assumed to be equal across relevant therapies (i.e., upadacitinib, tofacitinib, and biologics); however, more surveillance is expected with upadacitinib given its AE profile.
CADTH reanalysis results	• CADTH conducted reanalyses by applying the following changes: assuming an equal probability of clinical response, remission, and serious infection between upadacitinib and all relevant comparators, with no difference between low and high maintenance dosing. • Upadacitinib was strictly dominated by adalimumab (i.e., had equal QALYs and greater costs) in both the treatment-naive and treatment-experienced populations. Results of the CADTH reanalysis show conventional therapy and adalimumab on the cost-effectiveness frontiers. All other relevant comparators were strictly dominated. A price reduction is necessary for upadacitinib to be considered an optimal therapy at a WTP threshold of $50,000 per QALY, based on the CADTH reanalysis. • When only considering drug acquisition costs, a price reduction between 32% and 55% is necessary for upadacitinib to be no more costly than the least costly relevant comparator, depending on the dose of upadacitinib.

AE = adverse event; CEF = cost-effectiveness frontier; ICER = incremental cost-effectiveness ratio; IL = interleukin; JAK = Janus kinase; LY = life-year; QALY = quality-adjusted life-year; TNF = tumour necrosis factor; UC = ulcerative colitis; WTP = willingness to pay.

[a]Biologic refers to TNF alpha antagonists, integrin receptor antagonists, or interleukin 12/23 inhibitors.

Budget Impact

The sponsor estimated the budget impact of upadacitinib over 3 years. CADTH identified the following key limitations with the sponsor's analysis: uncertainty in the projected market uptake of upadacitinib, uncertainty in the projected capture rates of upadacitinib and model inflexibility to assess the impact of capturing market shares from comparators in different proportions than in the sponsor's base case, exclusion of costs associated with concomitant use of conventional therapy, and inclusion of copayments.

CADTH conducted a reanalysis excluding copayments, which estimated the budget impact of reimbursing upadacitinib to be $32,172 in year 1, $796,095 in year 2, and $1,873,060 in year 3, with a 3-year total of $2,636,982. CADTH notes that these estimates are associated with significant uncertainty, due to limitations associated with the projected uptake of upadacitinib as well as CADTH's inability to assess the impact of different projected capture rates from various comparators.

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: September 27, 2022

Regrets: Two expert committee members did not attend.

Conflicts of interest: None.

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