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CADTH Reimbursement Recommendation

Upadacitinib (Rinvoq)

Indication: For the treatment of adult patients with moderately to severely active Crohn disease who have demonstrated prior treatment failure; that is., an inadequate response to, loss of response to, or intolerance to at least one conventional and/or biologic therapy.

Sponsor: AbbVie Corporation

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Rinvoq?

CADTH recommends that public drug plans reimburse Rinvoq for the treatment of moderately to severely active Crohn disease (CD) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Rinvoq should only be covered to treat adult patients with moderately to severely active CD who do not respond to, stop responding to, or who cannot tolerate conventional or biologic therapies, provided that Rinvoq is covered for a similar patient population and in a similar way to biologic therapies currently reimbursed by public drug plans for the treatment of adult patients with moderately to severely active CD.

What Are the Conditions for Reimbursement?

Rinvoq should only be reimbursed if prescribed by a physician experienced in the diagnosis and management of CD, if it is not used in combination with biologics for CD, and if the cost of Rinvoq is reduced so that it does not cost the drug programs more than the least costly biologic therapy reimbursed for the treatment of moderately to severely active CD. Patients must respond to treatment in the first 12 weeks of starting Rinvoq to continue receiving the drug.

Why Did CADTH Make This Recommendation?

- Three clinical trials in patients with moderately to severely active CD who had inadequate response or were intolerant to prior conventional or biologic therapies were assessed in this review. In all of these trials, patients treated with Rinvoq showed an improved clinical remission and endoscopic response compared to patients treated with placebo.
- Rinvoq may meet some important needs of patients as it is an additional treatment option that induces and maintains disease remission and improves symptoms and health-related quality of life (HRQoL).
- 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 insufficient evidence to justify a greater cost for Rinvoq compared with other treatments reimbursed for treating moderately to severely active CD in adults.
- Based on public list prices, Rinvoq is estimated to cost the public drug plans approximately $67 million over the next 3 years.

Summary

Additional Information

What Is CD?

CD is an inflammatory bowel disease that causes recurrent uncontrolled inflammation in any part of the gastrointestinal tract, but commonly affects the small intestine, colon, and rectum. For many patients with CD, symptoms are chronic and sporadic, and disease severity can vary widely over time. Common CD symptoms include diarrhea, abdominal pain, fatigue, fever, rectal bleeding, loss of appetite, weight loss, and malnutrition. There is no cure for CD, and patients usually have symptoms on and off for life. It was estimated in 2018 that CD affects more than 135,000 people in Canada.

Unmet Needs in CD?

Patients with CD expressed a need for effective treatments that reduce symptoms, achieve sustained remission or response, reduce corticosteroid use, and improve HRQoL.

How Much Does Rinvoq Cost?

Treatment with Rinvoq is expected to cost between $23,074 and $30,178 per patient in the first year and $18,864 to $28,090 per patient in subsequent years.

Recommendation

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

Rationale for the Recommendation

Evidence from 3 phase III, double-blind, randomized, placebo-controlled trials (U-EXCEED, U-EXCEL, and U-ENDURE) showed that, compared with placebo, treatment with upadacitinib resulted in clinically meaningful improvements in the coprimary outcomes of clinical remission and endoscopic response after 12-week induction (45 mg daily, oral) and 52-week maintenance (15 mg or 30 mg daily, oral) in adult patients with moderately to severely active CD who have demonstrated prior treatment failure; that is, an inadequate response to, loss of response to, or intolerance to at least 1 conventional and/or biologic therapy. In induction trials, the difference compared to placebo in patients who achieved clinical remission based on patient-reported outcomes (PROs) was 25.9% (95% CI, 18.7% to 33.1%) in the U-EXCEED trial, and 28.7% (95% CI, 20.9% to 36.4%) in the U-EXCEL trial. For clinical remission based on the Crohn Disease Activity Index (CDAI), the differences compared to placebo were 17.9% (95% CI, 10.0% to 25.8%) in the U-EXCEED trial and 20.8% (95% CI, 12.7% to 28.8%) in the U-EXCEL trial. In patients who achieved clinical response in the induction trials and continued into the U-ENDURE maintenance trial, the between-group differences compared to placebo in clinical remission based on PROs at 52 weeks were 21.9% (95% CI, 13.7% to 30.0%) and 31.8% (95% CI, 23.2% to 40.3%) in the upadacitinib 15 mg group and upadacitinib 30 mg group, respectively, while the between-group differences compared to placebo in clinical remission based on CDAI, they were 23.7% (95% CI, 15.2% to 32.1%) and 32.8% (95% CI, 23.9% to 41.6%), respectively. Induction therapy with upadacitinib also resulted in clinical benefits in endoscopic remission, improvements in HRQoL, and the proportion with CR-100. In the induction trials, the difference in endoscopic response at 12 weeks compared to placebo was 31.2% (95% CI, 25.5% to 37.0%) in the U-EXCEED trial and 33.0% (95% CI, 26.2% to 39.9%) in the U-EXCEL trial, while in the U-ENDURE maintenance trial, the difference in endoscopic response at 52 weeks was 21.0% (95% CI 13.6%, 28.4%; $P < 0.0001$) and 33.7% (95% CI, 26.0% to 41.3%) in the upadacitinib 15 mg group and upadacitinib 30 mg group, respectively.

Patients and clinicians indicated that there is a need for effective treatments that reduce symptoms, achieve sustained remission or response using both clinical and endoscopic metrics, reduce corticosteroid use, and improve HRQoL. CDEC concluded that upadacitinib may address these needs, as it is effective in inducing and maintaining clinical remission and endoscopic response, reducing clinical symptoms, aiding in discontinuation of corticosteroids, and may improve HRQoL in adult patients who had an inadequate response, lost response, or experienced intolerance to other treatments.

At the sponsor-submitted price for upadacitinib and publicly listed prices for all relevant comparators, upadacitinib was more costly than several relevant comparator treatments used in moderately to severely

active CD. As there is insufficient evidence to suggest that upadacitinib is more effective than biologic treatments for moderately to severely active CD, the total drug cost of upadacitinib should not exceed the total drug cost of the lowest-cost biologic treatment.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Eligibility for upadacitinib should be based on the criteria used by each of the public drug plans for biologic therapies for the treatment of adult patients with moderately to severely active CD who have had an inadequate response, a loss of response, or intolerance to conventional or biologic therapies.	The results of the 3 placebo-controlled RCTs, U-EXCEL, U-EXCEED, and U-ENDURE, demonstrated that upadacitinib is an effective treatment for moderately to severely active CD who have had an inadequate response, a loss of response, or intolerance to conventional or biologic therapies. There is no evidence that upadacitinib should be held to a different standard than biologic therapies currently reimbursed for the treatment of adult patients with moderately to severely active CD when considering initiation of therapy.	The definition of moderately to severely active CD and inadequate response, intolerance, or loss of response to other therapies should align with those used for reimbursed biologics.
Renewal		
2. The patient must have achieved clinical response to induction therapy after 12 weeks of treatment to continue to maintenance therapy.	In the U-EXCEL and U-EXCEED induction trials, patients had to have a clinical response at the end of the induction period at week 12 to continue to the maintenance period in the U-ENDURE trial.	The definition of clinical response should align with the definitions used for reimbursed biologics; e.g., a reduction of CDAI score greater than or equal to 100 points, or an HBI score of 5 or less, or a decrease in HBI score of 4 or more. Endoscopic follow-up is not required if clinical response continues to be achieved. 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 surrogate markers such as fecal calprotectin and resolution of anemia can also be used. Ultimately, CDEC considered it appropriate to leave the determination of clinical response up to the treating physician's clinical judgment.
3. Assessment for renewal after the first assessment of treatment response should be performed every year. The patient must maintain clinical response to	Patients who lose response to upadacitinib are no longer benefiting from treatment.	—

Reimbursement condition	Reason	Implementation guidance
therapy to continue receiving upadacitinib.		
Prescribing		
4. Upadacitinib should only be prescribed by a physician experienced in diagnosing and managing CD.	It is important to ensure that upadacitinib is only prescribed for appropriate patients.	The clinical expert indicated that prescribing upadacitinib should not be limited to IBD specialists. General gastroenterologists would have the expertise required to initiate therapy, and general internists with a particular interest in IBD/GI may have sufficient experience and training to prescribe upadacitinib, which may be important for accessibility in rural and remote regions of Canada.
5. Upadacitinib should not be reimbursed when combined with biological or other JAK inhibitor treatments for CD.	There is no evidence to support the use of upadacitinib in combination with biological or other JAK inhibitor treatments for CD.	Upadacitinib may be used in conjunction with conventional therapy.
Pricing		
6. Upadacitinib should be negotiated so that it does not exceed the drug program cost of treatment with the least costly biologic treatment reimbursed for the treatment of moderately to severely active CD.	There is insufficient evidence to justify a cost premium for upadacitinib over the least costly relevant comparator reimbursed for moderately to severely active CD.	—
Feasibility of adoption		
7. The feasibility of the adoption of upadacitinib must be addressed.	At the submitted price, the incremental budget impact of upadacitinib is expected to be approximately $40 million in year 3. The magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption.	—

5-ASA = 5-aminosalicylates; CD = Crohn disease; CDAI = Crohn Disease Activity Index; HBI = Harvey-Bradshaw Index; IBD = inflammatory bowel disease; JAK = Janus kinase.

Discussion Points

- Upadacitinib provides another treatment option for CD. CDEC concluded that evidence from U-EXCEED, U-EXCEL, and U-ENDURE demonstrated that induction and maintenance therapy with upadacitinib was safe and well tolerated compared to placebo; however, all studies lacked active comparators. In addition, [redacted] CDEC was unable to determine the relative efficacy and safety of upadacitinib compared to biologic therapies in the Canadian setting.

- Patients described negative effects of CD on HRQoL. In both induction trials and the maintenance trial, assessment of HRQoL using the Inflammatory Bowel Disease Questionnaire (IBDQ) favoured upadacitinib over placebo, and the difference was considered to be clinically meaningful in the induction trials. It may be clinically meaningful in the maintenance trial.
- CDEC noted that some patients in the U-EXCEED and U-EXCEL trials did not achieve clinical response in the first 12-week induction period and then achieved clinical response after an additional 12 weeks of treatment with upadacitinib 30 mg. However, only patients who experienced clinical response to 12 weeks of treatment with upadacitinib 45 mg were eligible for randomization into the U-ENDURE maintenance trial. CDEC concluded that there is currently insufficient evidence to support an extended treatment with upadacitinib 30 mg for an additional 12 weeks if patients do not experience clinical response after the first 12-week induction treatment period with upadacitinib 45 mg.
- The oral route of administration of upadacitinib may be more convenient or preferred for patients than other therapies for CD (i.e., biologics), which are predominantly administered through IV infusion or subcutaneous injection.
- CDEC discussed that upadacitinib may also result in benefits in the discontinuation of corticosteroid use for CD and the resolution of extra-intestinal manifestations (EIMs) among patients who had EIMs at baseline. The clinical expert advised CDEC that the resolution of EIMs is of particular importance in the subgroups of patients who have significant EIMs that have a negative impact on HRQoL and who may have reduced options for therapies that have been shown to improve the resolution of EIMs.
- While evidence from the trials indicates that treatment with upadacitinib may result in little to no difference in CD-related hospitalizations or [redacted] at 12 or 52 weeks when compared with placebo, the clinical expert advised CDEC that the duration of the study may be inadequate to evaluate a difference in these outcomes.
- CDEC heard from the clinical expert that clinicians may be more likely to use upadacitinib 30 mg rather than upadacitinib 15 mg as a maintenance dosage. However, CDEC discussed that the cost-effectiveness of upadacitinib 30 mg compared to upadacitinib 15 mg is uncertain and that there is insufficient evidence to justify a cost premium for upadacitinib 30 mg in comparison with upadacitinib 15 mg.

Background

CD is a chronic progressive form of inflammatory bowel disease (IBD) that leads to significant disability and has a negative impact on a patient's HRQoL. It is characterized by recurrent, uncontrolled inflammation that can affect any part of the gastrointestinal (GI) tract from mouth to anus and mostly affects the ileum, colon, and rectum. Common CD symptoms include diarrhea, abdominal pain, fatigue, fever, rectal bleeding, loss of appetite, weight loss, and malnutrition. Complications associated with CD can include bowel obstructions, fistulas, anal fissures, intra-abdominal and other abscesses, and ulcers. For many patients with CD, symptoms are chronic and intermittent, and disease activity and severity can vary widely over time. The incidence of CD varies across the Canadian provinces, with the highest rate reported in Nova Scotia at 22.6

per 100,000 persons. In contrast, in Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan, rates range from 8.8 to 16.6 per 100,000 persons. The predicted prevalence of CD in 2018 was 368 per 100,000 population, which translates to approximately 135,000 people in Canada living with CD.

Currently, there is no cure for CD. Therapeutic goals include inducing and maintaining clinical and endoscopic remission and reducing corticosteroid dependence. There are 2 significant categories of pharmacotherapies used for treating CD: conventional therapies and biologic therapies. The conventional therapies include corticosteroids (e.g., prednisone), 5-aminosalicylates (5-ASA), and immunomodulators (e.g., azathioprine, cyclosporine, methotrexate, and 6-mercaptopurine). Medical management is based on a stepwise approach, with treatments used sequentially and escalated to either newer therapies or higher doses as patients fail to respond to each treatment step. Not all patients respond to available treatments, and their disease may become refractory to the current treatment regimens.

Upadacitinib is a selective and reversible Janus kinase (JAK) inhibitor engineered to have greater inhibitory potency for JAK1 versus JAK2, JAK3, and TYK2 in human cellular assays. Upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2. Upadacitinib is administered orally. The recommended dosing schedule is in 2 phases: a 12-week induction phase consisting of 45 mg upadacitinib once daily, followed by an ongoing maintenance phase. The recommended dose of upadacitinib for maintenance treatment for patients who are in the age group 18 to 64 years of age is 15 mg or 30 mg once daily, based on patient presentation where the dose of 30 mg once daily may be appropriate for patients with high disease burden (such as refractory or severe disease) or those who do not show adequate therapeutic benefit with 15 mg once daily, and the lowest effective dose for maintenance should be used. For patients who are at least 65 years of age, the recommended maintenance dose is 15 mg once daily. In patients who are responding to induction or maintenance treatment with upadacitinib, corticosteroids may be reduced and/or discontinued following standard of care.

Upadacitinib is indicated for the treatment of adult patients with moderately to severely active CD who have demonstrated prior treatment failure; that is, an inadequate response to, loss of response to, or intolerance to at least 1 of conventional and/or biologic therapy.

Sources of Information Used by the Committee

To make its recommendation, CDEC considered the following information:

- a review of 3 randomized controlled trials (RCTs) in adult patients with moderate to severe CD
- patients perspectives gathered by 2 patient groups, Crohn and Colitis Canada (CCC) and the GI Society
- input from public drug plans that participate in the CADTH review process
- a clinical specialist's perspective, who has expertise in diagnosing and treating patients with CD
- input from 1 clinician group, the Canadian IBD Specialist Group
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from 1 clinical expert who CADTH consulted for this review.

Patient Input

Two patient groups, the CCC and the GI Society, provided input for this review. The CCC gathered the information from a report published in 2018 (Impact of IBD in Canada Report), a survey, and interviews with patients who participated in upadacitinib clinical trials. The patient input provided by the GI Society was based on surveys, interviews, a patient roundtable, and media interactions.

The 2 patient groups emphasized that CD has a tremendous impact on every aspect of a person's life. The most frequent symptoms associated with CD reported by the patients are diarrhea, rectal bleeding, abdominal pain, and weight loss. Other symptoms included inflammation of the eyes or joints, ulcers of the mouth or skin, tender and inflamed nodules on the shins, anemia, anxiety, and stress. Both the CCC and GI Society stated that being unable to predict when the next urgency of bowel movements would occur and the inability to control the flare had a significant negative impact on the personal and social lives of patients with CD.

The GI Society described the treatment of CD as multifaceted as it involves managing symptoms and consequences of the disease and reducing inflammation. Patients also rely on medications to reduce the need for surgery. First-line treatments include 5-ASA and corticosteroids to reduce inflammation in moderate to severe cases of CD. When 1 medication fails, patients must try another one. According to the patient input, these treatments are inconvenient therapies that make it difficult for patients to keep a normal routine. As described by the GI input society, JAK inhibitors (such as the drug under review) are a newer class of medication. Unlike biologics, which are delivered by infusion therapy, JAK inhibitors are more accessible and more convenient to take since they are in pill form. Patients have difficulty achieving remission or adequate symptom relief despite available treatment options. Even after surgery to repair fistulas and fissures or the removal of diseased bowel tissue, CD symptoms tend to reoccur in most patients.

Improved outcomes noted as important by the patient groups included symptom mitigation and a reduction in preventable patient suffering. CCC respondents also noted that managing unpredictable and frequent bowel movements, pain, and fatigue was important. The CCC noted that unmet patient needs varied among individuals depending on their unique symptoms and life circumstances. Both patient groups emphasized the importance of a treatment option that is easy to administer and one that can provide symptom relief, achieve remission, and improve subsequent HRQoL.

Three patients from the CCC and 2 patients from the GI Society group had experience with upadacitinib and reported near-immediate improvements in their health, alleviation of the disease symptoms, and symptoms of their CD with no side-effects or few mild side-effects such as weight gain. Patients noted the convenience of pill-based administration and no need to refrigerate the medication or visit a clinic for infusions.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

The clinical expert indicated there are profound treatment gaps in the management of IBD, including CD. Transmural damage results over time, leading to complications (e.g., stenosis and penetrating complications that often require surgery). Early treatment initiation is key to limit the disease activity and stop progression. Although there are a number of effective drugs available for the treatment of moderate to severe CD, there are significant limitations in efficacy, in addition to the frequency of loss of response over time and the reduced efficacy with the introduction of each subsequent biologic after failure. This was described as the greatest treatment challenge in the management of CD.

The clinical expert described that primary nonresponse and secondary loss of response are common in treating CD with advanced therapies, and therefore, therapies that remain efficacious in biologic-experienced patients are needed.

Clinical trial design historically focused on clinical symptoms of response and remission, which may not always correlate with objective measures such as endoscopic remission and mucosal healing. The clinical expert noted that long-term longitudinal studies to evaluate the modification of bowel damage are lacking as most clinical trials are up to 2 years in duration.

The clinical expert described that some treatments are particularly inconvenient and impact a patient's lifestyle due to the need to go to an infusion clinic for a few hours every 4 to 8 weeks. Therapies given by subcutaneous (SC) injection are more convenient, but patients may find them painful. There are currently no available orally-administered advanced therapies for CD.

The clinical expert noted that the current treatment paradigm for adults with moderately to severely active CD is complex and is dictated by disease phenotype. Conventional therapies (e.g., steroids and immune suppressants) are not typically used in isolation long-term, and most patients with moderate to severe active disease would go on to receive advanced therapy such as biologic therapy. The clinical expert noted that the first-prescribed therapy has the best chance for improvement and healing due to the aforementioned pattern of lower likelihood of robust response with subsequent advanced therapies. Selecting the most optimal therapy from the start is a challenge and is based on disease phenotype, disease severity, and the risks and expected onset of action of each available therapy; for instance, particularly severe disease would warrant the selection of a therapy with rapid onset, high efficacy, and steroid-sparing effects (e.g., antiTNFs or anti IL 23 and 12/23).

Nearly half of patients have EIMs of CD, which can be disabling, and only a select few currently available medications address them, with a preference for the antiTNF category. Approximately a quarter of CD patients have fistulizing perianal disease, which is a marker of severe disease, and again antiTNFs are the preferred therapeutic option for this subpopulation. Other options for patients with these disease phenotypes are needed.

The clinical expert indicated that upadacitinib would be used as a first drug for patients receiving advanced therapies for CD, and that there is no mechanistic, efficacy, or sequencing-based argument to require the failure of other advanced drugs before initiating upadacitinib.

The clinical expert also noted that there is increasing off-label use of combination therapies with complementary mechanisms of effect in particularly severe, high-risk patients with prior drug failures, surgeries, or other markers of disabilities. The expert described that combinations would typically include a low-risk, safe drug such as an anti-integrin with other more systemically active drugs. This may become relevant in the case of upadacitinib. However, it was emphasized that this is limited to dire situations where there is a risk of extensive surgery or disability.

The clinical expert described that patients with confirmed pathologic or histologic diagnosis of moderate to severe CD are typically diagnosed by a gastroenterologist. Misdiagnosis is rare, but diagnosis may be delayed as previously described. Patients with EIMs (e.g., inflammatory arthropathy, peripheral or axial) are a priority for treatment. Although there are no clear stages of CD, objective measures such as endoscopic activity and the requirement or dependence on corticosteroids are important while the presence of clinical symptoms is not as critical. There are no established predictors of disease response.

The clinical expert noted that assessment of response in clinical practice differs from clinical trials due to logistics and patient preference. The most easily accessed marker of response is improvement in clinical symptoms (especially abdominal pain and frequency of soft or liquid stools), but this is poorly correlated with objective markers of disease activity and may be very heterogeneous according to disease phenotype. For instance, patients with bowel stricture may experience constipation instead of diarrhea, and patients with prior surgeries may have differing symptoms caused by anatomic alteration rather than inflammation. Objective measures of disease activity are important, especially endoscopy (i.e., ileocolonoscopy). The clinical expert described that although the clinical trials assessed endoscopic outcomes at 12 weeks, endoscopy is rarely performed at 12 weeks in clinical practice, and instead is typically performed at 6 to 9 months and can be challenging to repeat. Other objective measures may include biomarkers (c-reactive protein [CRP] and fecal calprotectin) as well as noninvasive intestinal ultrasound.

The clinical expert indicated the treatment discontinuation should be considered similarly to other advanced therapies for adults with CD, a combination of clinical symptoms and objective data to support primary nonresponse or loss of response:

- Persistence or worsening of clinical symptoms, most importantly diarrhea and abdominal pain.
- Persistence or worsening of endoscopic activity.
- Worsening or persistent elevation of biomarkers including CRP and fecal calprotectin.
- Worsening or development of complications (including strictures and penetrating disease) on cross-sectional imaging.
- Dependence on or need for recurrent courses of corticosteroids (e.g., 2+ full courses of oral prednisone within 1 year), but details may be debated.

- Development of adverse events (AEs) should be weighed on case-by-case basis depending on treatability and severity of the AE. All patients should be vaccinated appropriately (e.g., varicella) to avoid any preventable AEs potentially associated with treatment.
- There are circumstances when patients with severe disease may require a course of corticosteroids (a single course), which may not again preclude ongoing maintenance and thus, the need for discontinuation would be judged by the treating physician.

Prescription of upadacitinib should not be limited to IBD specialists, as general gastroenterologists would have the expertise required to initiate therapy. General internists with a special interest in IBD/GI may have sufficient experience and training to prescribe upadacitinib, which may be important for accessibility in rural regions of Canada.

The clinical expert noted that initiation criteria should be similar to that of biologics currently reimbursed for the treatment of adult patients with moderately to severely active CD. However, the expert emphasized that the current requirements for previously failed therapies are not up-to-date with clinical practice. In particular, the current requirements for prior drug failures in prescribing advanced therapies includes 5-ASA, which is considered by the clinical expert to be out-of-date due to its known lack of efficacy in this population. The clinical expert noted that in clinical practice, this results in short prescriptions of 5-ASA to meet the requirements when it is not expected to have patient benefit, and the expert recommended that this is not included as a requirement for prior treatment failures when prescribing upadacitinib. The expert noted that if treatment is interrupted for at least 2 weeks, the patient may need to undergo induction therapy again.

Clinician Group Input

One clinician group, the Canadian IBD Specialist Group, responded to CADTH's call for input. The input was based on a discussion held by the Canadian IBD Specialist Group in March 2023.

The clinician group emphasized that CD tremendously impacts the physical, emotional and social aspects of those living with the disease, affecting the HRQoL and causing a significant economic burden. The current treatment paradigm for CD includes 5-ASA, corticosteroids, immune modifiers, and biologics that include antiTNF, anti-integrin, and anti-IL 12/23 and anti-IL 23 drugs.

The input from the clinician groups identified the same unmet medical needs for CD patients and potential place in therapy for the drug under review as the clinical experts consulted by CADTH.

The clinician group noted that there are significant unmet therapeutic needs for patients living with moderate to severe CD. There is a lack of safe and effective treatments that could rapidly improve the endoscopic appearance, maintain long-term improvement and remission, and reduce the risk of complications and the need for surgery.

In addition to relieving clinical symptoms, the clinician group emphasized that the goal of treatment should focus on changing the course of disease for CD patients, preventing further intestinal damage, avoiding disability, and reducing the overall cost of care.

The clinician groups noted that upadacitinib has a new mechanism of action, and it is the first oral therapy for CD that has ever been evaluated to meet the treatment goals. According to the clinician group, any patient with inadequate response or intolerance to corticosteroids or multiple advanced therapies and those with 1 or more extraintestinal IBD manifestations could benefit from upadacitinib.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially have an impact on the implementation of a CADTH recommendation for upadacitinib:

- considerations for relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- system and economic issues.

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	
Pivotal trials were placebo-controlled. There are no direct head-to-head trials with other therapies used for the treatment of CD. Would other active therapies have been a more informative comparator?	CDEC and the clinical expert indicated that there are several other advanced therapies for adults with moderately to severely active CD for which there is a lack of head-to-head data with upadacitinib, and a head-to-head comparison between upadacitinib and other advanced therapies would have been more informative.
Considerations for initiation of therapy	
Should eligibility criteria for upadacitinib be based on the initiation criteria used by each of the public drug plans for biologic treatments currently reimbursed for the treatment of adult patients with moderately to severely active CD who have had an inadequate response, a loss of response, or intolerance to conventional and/or biologic therapies?	CDEC and the clinical expert agreed that the initiation criteria should be similar to existing criteria for biologic treatments currently reimbursed for the treatment of adult patients with moderately to severely active CD who have had an inadequate response, a loss of response, or intolerance to conventional and/or biologic therapies. The clinical expert noted that there is a caveat with the current initiation criteria for the biologic treatments which require previous treatment with 5-ASA which according to the clinical expert is known to be an ineffective therapy in this population. The clinical expert noted that initiation criteria for upadacitinib and other advanced or biologic therapies for this population should not require prior experience with 5-ASA.

Implementation issues	Response
Considerations for continuation or renewal of therapy	
Should renewal criteria for upadacitinib be based on the renewal criteria used by each of the public drug plans for biologic treatments currently reimbursed for the treatment of adult patients with moderately to severely active CD?	CDEC and the clinical expert agreed that the renewal criteria should be similar to the renewal criteria used by each of the public drug plans for biologic treatments currently reimbursed for the treatment of adult patients with moderately to severely active CD.
Considerations for discontinuation of therapy	
Does induction need to be repeated if there is an interruption in treatment?	The clinical expert noted that induction needs to be repeated if there is an interruption of 2 weeks or more. However, CDEC noted that there is no evidence available for re-induction in the event of interruption in treatment.
Should discontinuation criteria for upadacitinib be based on the discontinuation criteria used by each of the public drug plans for biologic treatments currently reimbursed for the treatment of adult patients with moderately to severely active CD?	CDEC and the clinical expert agreed that the discontinuation criteria should be similar to the discontinuation criteria used by each of the public drug plans for biologic treatments currently reimbursed for the treatment of adult patients with moderately to severely active CD.
Should patients achieve clinical response to induction therapy after 12 weeks of treatment with upadacitinib to continue to maintenance therapy?	CDEC and the clinical expert agreed that induction patients should achieve clinical response to induction therapy after 12 weeks of treatment with upadacitinib to continue maintenance therapy with upadacitinib.
Considerations for prescribing of therapy	
Is it appropriate to use upadacitinib in combination with other JAK inhibitors or biologics? Are there any concerns for clinical practice?	The clinical expert noted that there is increasing off-label use of combination therapies with complementary mechanisms of effect in particularly severe, high-risk patients with prior drug failures, surgeries, or other markers of disabilities. Combinations would typically include a low-risk, safe drug such as an anti-integrin with other more systemically active drugs. It is important to note that combination therapies such as this would be limited to dire situations where there is a risk of extensive surgery or disability. The clinical expert also noted that upadacitinib should not be combined with other therapies that are higher risk, more systematically active drugs such as other JAK inhibitors. CDEC noted that there is no evidence available for the use upadacitinib in combination with other JAK inhibitors or biologics for the treatment of CD and recommended that upadacitinib should not be reimbursed when used in combination with biologic or other JAK inhibitor treatments for CD.
Should upadacitinib only be prescribed by a physician experienced in the diagnosis and management of CD?	CDEC agreed with the clinical expert that prescribing of upadacitinib should not be limited to IBD specialists, as general gastroenterologists would have the expertise required to initiate therapy. The clinical expert also noted that general internists with a special interest in IBD/GI may have sufficient experience and training to prescribe upadacitinib, which may be important for accessibility in rural regions of Canada.

Implementation issues	Response
Care provision issues	
Upadacitinib has a black box warning for an increased risk of infections, malignancy and thromboses, as these events have been reported. Canadian labelling for all JAK inhibitors was updated in November 2022 to include the risk of serious heart-related problems, thrombosis, and malignancies. This precautionary measure was based on a Health Canada review of tofacitinib and whether these risks would apply to baricitinib and upadacitinib.	Comment from the drug plans to inform CDEC deliberations.
System and economic issues	
There are negotiated confidential prices for the biosimilars of adalimumab and infliximab. There is also a negotiated price for vedolizumab. Is there any reason a public plan should pay a significant price premium for upadacitinib?	Comment from the drug plans to inform CDEC deliberations.
The submission for upadacitinib includes the marketed price for a 45 mg tablet; however, there is no 45 mg tablet marketed or approved by Health Canada. Currently only the 15 mg and 30 mg tablets are marketed. The included price is $101.8100 per 45 mg tablet. Will the 45 mg strength be marketed in Canada?	The sponsor confirmed that the 45 mg tablet is currently approved and marketed in Canada. The DIN is 02539721. CDEC noted that the dosage of upadacitinib should not exceed 45 mg daily during induction, and that the induction with the 45 mg daily dosage should not continue beyond 12 weeks. CDEC also noted that during the maintenance period, the dosage of upadacitinib should not exceed 30 mg daily in patients who are in the age group 18 to 64 years of age, and for patients who are at least 65 years of age, the dosage of upadacitinib should not exceed 15 mg daily.

5-ASA = 5-aminosalicylates; CD = Crohn disease; IBD = inflammatory bowel disease; JAK = Janus kinase.

Clinical Evidence

Systematic Review

Description of Studies

Three phase III, double-blind, placebo-controlled, multicentre, international RCTs were included in this review. Two of the RCTs were induction studies in adult patients with moderately to severely active CD and a history of biologic failure (U-EXCEED) or history of biologic and/or conventional therapy failure (U-EXCEL). Patients in both induction studies were randomized in a 2:1 ratio to receive upadacitinib 45 mg once daily or placebo. The primary results for randomized cohorts were evaluated at 12 weeks (part 1). However, patients who did not achieve an adequate response could carry on to part 2 or 3 for extended induction, where adequate response was defined as at least a 30% decrease in average daily very soft or liquid stool frequency and/or at least 30% decrease in average daily abdominal pain score (both not worse than baseline). The third RCT was a maintenance study of upadacitinib 15 mg or 30 mg once daily versus placebo in patients who had achieved adequate response in either the U-EXCEED or U-EXCEL trial, and the primary results were evaluated at 52 weeks among re-randomized patients from part 1 of the induction studies. Patients who had carried on

to extended induction therapy in either of the induction study and thereafter achieved a response could also enrol into cohort 2 or 3 of the U-ENDURE trial, which were not randomized. The coprimary outcomes in all trials included clinical remission (based on patient-reported outcomes [PROs] or the Crohn Disease Activity Index [CDAI]), and endoscopic response (based on the Simple Endoscopic Score for Crohn Disease [SES-CD]). Other important outcomes included endoscopic remission, proportion of patients who discontinued corticosteroid use for CD and achieved clinical remission (among patients taking corticosteroids at induction baseline), proportion of patients who achieved both clinical remission and endoscopic remission, change in HRQoL (using the IBDQ), clinical response [CR]-100, resolution of EIMs in patients who had EIMs at induction baseline, the proportion who experienced CD-related hospitalizations or surgeries, and the proportion who experienced harms including serious adverse events (SAEs) or adverse events of special interest (AESIs).

U-EXCEED enrolled 624 patients across 229 sites in 39 countries; U-EXCEL enrolled 526 patients across 209 sites in 42 countries; and U-ENDURE enrolled 901 patients across 277 sites in 43 countries. In the double-blind cohorts of U-EXCEED, U-EXCEL, and U-ENDURE, there were slightly more male than female patients (53.5%, 53.8%, and 55.4%), and the mean ages were 38.1, 39.6, and 37.0 years, respectively. Most enrolled patients were white (approximately 70% in each trial, followed by Asian, Black, multiple races (unspecified in the study), and American Indian or Alaska Native). The mean duration of CD was 9.4 years in U-EXCEED, 6.1 years in U-EXCEL, and 7.2 years in U-ENDURE; the differences were expected given that U-EXCEL included patients who may not have failure with biologics, indicating an earlier point in treatment history on average. Overall, most enrolled patients in the randomized cohorts had a history of biologic failure (100% in U-EXCEED by design, 45.4% in U-EXCEL, and 75.6% in U-ENDURE).

Efficacy Results: Induction

Induction Outcomes (12 Weeks)

Clinical Remission per PROs at 12 Weeks

In U-EXCEED and U-EXCEL, there was a higher percentage of patients who achieved clinical remission per PROs among those treated with upadacitinib 45 mg than placebo. In U-EXCEED, the response rate difference compared to placebo was 25.9% (95% CD: 18.7% to 33.1%), and in U-EXCEL it was 28.7% (95% CI, 20.9% to 36.4%).

Results were consistent across subgroups based on number of prior biologics failed and the analysis for clinical remission per PROs at 12 weeks.

Clinical Remission per CDAI at 12 Weeks

In U-EXCEED and U-EXCEL, there was a higher percentage of patients who achieved clinical remission per CDAI among patients treated with upadacitinib 45 mg than placebo. In U-EXCEED, the response rate difference compared to placebo was 17.9% (95% CI, 10.0% to 25.8%) and in U-EXCEL it was 20.8% (95% CI, 12.7% to 28.8%).

Results were consistent across subgroups based on number of prior biologics failed and the analysis for clinical remission per CDAI at 12 weeks.

Endoscopic Response at 12 Weeks

In U-EXCEED and U-EXCEL, there was a higher percentage of patients who achieved endoscopic response among patients treated with upadacitinib 45 mg compared to placebo. In U-EXCEED, the response rate difference compared to placebo was 31.2% (95% CI, 25.5% to 37.0%) and in U-EXCEL it was 33.0% (95% CI, 26.2% to 39.9%).

Results were consistent across subgroups based on number of prior biologics failed and the analysis for endoscopic response at 12 weeks.

Endoscopic Remission at 12 Weeks

In U-EXCEED and U-EXCEL, there was a higher percentage of patients who achieved endoscopic remission among patients treated with upadacitinib 45 mg than placebo. In U-EXCEED, the difference compared to placebo was 16.8% (95% CI, 12.0% to 21.6%) and in U-EXCEL it was 21.8% (95% CI, 15.8% to 27.8%).

Discontinuation of Corticosteroid Use and Clinical Remission per CDAI at 12 Weeks Among Patients Taking Corticosteroids at Baseline

In U-EXCEED and U-EXCEL, a higher proportion of patients treated with upadacitinib 45 mg discontinued corticosteroid use and had CDAI clinical remission at week 12 compared to the placebo group. In U-EXCEED, the difference compared to placebo was 22.5% (95% CI, 11.1% to 34.0%) and in U-EXCEL it was 27.7% (95% CI, 15.7% to 39.8%).

Results were similar for discontinuation of corticosteroid use and clinical remission per PROs at 12 weeks.

Clinical Remission per CDAI and Endoscopic Remission at 12 Weeks

In U-EXCEED and U-EXCEL, a higher proportion of patients treated with upadacitinib 45 mg had clinical remission per CDAI and endoscopic remission at 12 weeks. The adjusted difference compared to placebo was [redacted] and [redacted], in U-EXCEED and U-EXCEL, respectively.

Results were similar for clinical remission per PROs and endoscopic remission at 12 weeks.

Change from Baseline in IBDQ Total Score at 12 Weeks

In U-EXCEED and U-EXCEL, there was a larger within-group change from baseline in IBDQ total score in patients treated with upadacitinib 45 mg than patients treated with placebo. The between-group difference compared to placebo (least squared mean) was 24.3 (95% CI, 17.2 to 31.5) in U-EXCEED and 21.8 (95% CI, 15.6 to 28.1) in U-EXCEL.

CR-100 at 12 Weeks

In U-EXCEED and U-EXCEL, there was a higher percentage of patients who achieved CR-100 among patients treated with upadacitinib 45 mg than placebo. In U-EXCEED, the difference compared to placebo was 22.8% (95% CI, 14.4% to 31.2%), and in U-EXCEL it was 19.8% (95% CI, 11.3% to 28.4%).

Resolution of EIMs at 12 Weeks in Patients with EIMs at Baseline

In U-EXCEED, resolution of EIMs at week 12 in patients with any EIMs at baseline was 32.8% for upadacitinib 45 mg versus 21.7% for PBO (between-group difference 11.5%; 95% CI, −1.5% to 24.4%). In U-EXCEL,

resolution of EIMs at week 12 in patients with any EIMs at baseline was 28.5% for upadacitinib 45 mg versus 20.9% for PBO (between-group difference 9.0%; 95% CI, −1.9% to 19.9%). In both cases, the 95% CI crossed the threshold between potential benefit and potential harm (i.e., null).

Proportion With CD-Related Hospitalizations Through 12 Weeks

There were no substantial differences observed in the proportion of patients with CD-related hospitalizations between patients treated with upadacitinib 45 mg in U-EXCEED (20/324) and U-EXCEL (13/350) compared to patients treated with placebo (15/171 and 9/176), respectively. The difference compared to placebo was −2.6% (95% CI, −7.6% to 2.4%) in U-EXCEED and −1.4% (95% CI, −5.2% to 2.4%) in U-EXCEL, respectively. In both cases, the 95% CI crossed the threshold between potential benefit and potential harm (i.e., null).

Proportion With CD-Related Surgeries Through 12 Weeks

[redacted]

Maintenance Outcomes (52 Weeks)

Clinical Remission per PROs at 52 Weeks

In U-ENDURE, the upadacitinib 15 mg group and 30 mg group had higher percentages of patients who achieved response rates in clinical remission per PROs compared to the placebo group. The differences between upadacitinib 15 mg group and placebo, and between upadacitinib 30 mg group and placebo were 21.9% (95% CI, 13.7% to 30.0%) and 31.8% (95% CI, 23.2% to 40.3%), respectively.

The results were similar for the subgroups of at least 1 prior biologic failed, 1 prior biologic failed, and 0 prior biologics failed in the 30 mg group. However, for the subgroup of 0 prior biologics failed in the 15 mg group, the difference (versus placebo) was smaller and the 95% CI crossed the null value (11.7% [-9.1% to 32.5%]).

Clinical Remission per CDAI at 52 Week

The upadacitinib 15 mg group and 30 mg group had higher percentages of patients who achieved clinical remission per CDAI compared to the placebo group. The differences between upadacitinib 15 mg group and placebo, and between upadacitinib 30 mg group and placebo were 23.7% (95% CI, 15.2% to 32.1%) and 32.8% (95% CI, 23.9% to 41.6%), respectively.

Results in the subgroups based on number of prior biologics failed were consistent with the analysis for both dosage groups.

Endoscopic Response at 52 Weeks

The upadacitinib 15 mg group and 30 mg group had higher percentages of patients who achieved endoscopic response compared to the placebo group. The differences between upadacitinib 15 mg group and placebo, and between upadacitinib 30 mg group and placebo were 21.0% (95% CI, 13.6% to 28.4%) and 33.7% (95% CI, 26.0% to 41.3%), respectively.

Results in the subgroups based on number of prior biologics failed were consistent with the analysis for both dosage groups.

Endoscopic Remission at 52 Weeks

The upadacitinib 15 mg group and 30 mg group had higher percentages of patients who achieved endoscopic remission compared to the placebo group. The differences between upadacitinib 15 mg group and placebo, and between upadacitinib 30 mg group and placebo were 14.4% (95% CI, 7.7% to 21.0%) and 23.6% (16.1% to 31.0%), respectively.

Discontinuation of Corticosteroid Use at Least 90 Days Prior to Week 52 and Clinical Remission Per CDAI at 52 Weeks Among Patients Taking Corticosteroids for CD at Induction Baseline

Among patients taking corticosteroids for CD at induction baseline, a higher proportion of patients in the upadacitinib 15 mg group and 30 mg group discontinued corticosteroid use and had CDAI clinical remission at week 52 compared to the placebo group. The differences between upadacitinib 15 mg group and placebo, and between upadacitinib 30 mg group and placebo were 35.4% (95% CI, 23.3% to 47.5%) and 32.3% (95% CI, 20.1% to 44.5%), respectively. Among all patients (i.e., not limited to those taking corticosteroids at induction baseline), the differences between upadacitinib 15 mg group and placebo, and between upadacitinib 30 mg group and placebo were 23.8% (95% CI, 15.5% to 32.1%) and 32.2% (95% CI, 23.4% to 40.9%), respectively.

Clinical Remission per CDAI and Endoscopic Remission at 52 Weeks

A higher proportion of patients in the upadacitinib 15 mg group and 30 mg group had both CDAI clinical remission and endoscopic remission at week 52 compared to the placebo group. The differences between upadacitinib 15 mg group and placebo, and between upadacitinib 30 mg group and placebo were 12.2% (95% CI, 6.3% to 18.1%) and 19.8% (95% CI, 13.0% to 26.6%), respectively.

Change from Baseline in IBDQ Total Score at 52 Weeks

There was a larger within-group change from baseline in IBDQ total score in upadacitinib-treated patients (15 mg or 30 mg) than placebo-treated patients. The between-group difference (least squared mean) was 12.9 (95% CI, 4.3 to 21.4) when upadacitinib 15 mg group was compared to placebo and 18.1 (95% CI, 9.8, 26.4) when upadacitinib 30 mg group was compared to placebo. Only the between-group difference in the latter comparison (i.e., 30 mg upadacitinib versus placebo) was greater than the minimally important difference (MID) of 16 points in the IBDQ total score for patients with CD; the 95% CIs of both comparisons include values both greater than and less than this MID.

CR-100 at 52 Weeks

There was a higher percentage of patients who achieved CR-100 among patients treated with upadacitinib 30 mg or 15 mg than placebo. The differences between upadacitinib 15 mg group and placebo, and between upadacitinib 30 mg group and placebo were 27.1% (95% CI, 18.3% to 35.8%), and 36.4% (95% CI, 27.5% to 45.2%), respectively.

Resolution of EIMs at 52 Weeks in Patients with EIMs at Induction Baseline

The proportion who achieved resolution of EIMs at week 52 in patients with any EIMs at induction baseline was 24.6% (upadacitinib 15 mg), 35.6% (upadacitinib 30 mg), and 15.2% (placebo). The difference versus placebo was 9.6% (95% CI, −3.4% to 22.6%) for upadacitinib 15 mg and 22.0% (95% CI, 9.3% to 34.8%) for

upadacitinib 30 mg. For the 15 mg dose but not the 30 mg dose, the 95% CI crossed the threshold between potential benefit and potential harm (i.e., null).

Proportion With CD-Related Hospitalizations Through 52 Weeks

There were no substantial differences observed in the percentages of patients experienced CD-related hospitalizations across the upadacitinib 30 mg group, 15 mg group, and placebo group. The differences between upadacitinib 15 mg group and placebo, and between upadacitinib 30 mg group and were −0.78% (95% CI, −10.4% to 8.8%) and −4.17 (95% CI, −13.1% to 4.7%), respectively. In both cases, the 95% CI was wide and crossed the threshold between potential benefit and potential harm (i.e., null).

Incidence of CD-Related Surgeries Through 52 Weeks

[redacted]

Harms Results

Across the trials, AEs were common and were experienced by approximately 58% to 76% of patients. In the placebo-controlled parts of the trials, the rate of AEs and withdrawal due to AEs were generally similar between treatment arms. SAEs occurred to approximately 7% to 15% of patients across the different treatment arms and cohorts of the included trials and were approximately similar between upadacitinib-treated and placebo-treated patients in the comparative cohorts. Some of the most frequently reported SAEs among all trials were GI disorders and infections and infestations.

SAEs were evaluated using GRADE, and it was determined that upadacitinib induction or maintenance may result in little to no difference in the incidence of SAEs compared to placebo in a 12-week or 52-week time period.

AESIs were selected based on safety concerns reported for other JAK inhibitors, upadacitinib data obtained from preclinical studies, the upadacitinib development program, as well as customary regulatory concerns for novel small molecule drugs. Across the trials, AESIs of serious infection, opportunistic infection, herpes zoster, adjudicated gastrointestinal perforation, anemia, neutropenia, lymphopenia, creatine phosphokinase (CPK) elevation, hepatic disorder, renal dysfunction, and adjudicated venous thromboembolic events were observed. The most commonly reported AESIs (≥ 4% in any part or cohort of any included trial) included anemia, lymphopenia, serious infections, infections and infestations, herpes zoster, hepatic disorder, and CPK elevation. One adjudicated cardiovascular event was observed in U-EXCEL in a placebo-treated patient from part 1. Malignancies (all types), malignancies (excluding non-melanoma skin cancer), and non-melanoma skin cancer occurred rarely in U-ENDURE and were not observed in the induction trials (i.e., U-EXCEED and U-EXCEL). No events of lymphoma or active tuberculosis were observed in any included trial.

Critical Appraisal

All 3 trials were phase III, double-blind, placebo-controlled, multicentre studies that assessed several important clinical, endoscopic, and HRQoL-related outcomes. There were no concerns about internal validity related to study design (e.g., method of randomization, concealment of allocation, maintenance

of blinding, balance of patient characteristics between treatment arms, etc.). The U-ENDURE maintenance study included an enriched population given that only patients with response and adequate tolerance of study drug during induction could enrol, but this is representative of the reality of clinical practice. The trials all included nonrandomized cohorts to accommodate for patients who needed greater than 12 weeks of induction to reach an adequate response; although not represented in the primary analysis, these patients do also reflect a minority of real-world practice. Only the randomized data are discussed in detail herein. In U-ENDURE, patients who enrolled after achieving a response at 12 weeks of induction were re-randomized, which preserved the strength of the randomized study design. Additionally, the use of separate induction and maintenance studies is consistent with European Medicines Agency guidance for developing drugs for treating CD. Discontinuation rates were potentially imbalanced with a greater number of placebo-arm withdrawals due to the lack of efficacy in U-EXCEL and were generally high during U-ENDURE (20% to 28% across cohorts and treatment arms).

The clinical expert consulted by CADTH indicated that the study populations were wholly representative of the target population of adults with moderate to severe CD and a history of treatment failure. The dose of the intervention, upadacitinib, was 45 mg once daily during the induction studies and either 15 mg or 30 mg once daily during the maintenance study. The clinical expert consulted by CADTH described that clinical practice in moderate to severe CD would lean more commonly toward a 30 mg once daily maintenance dose due to evidence of higher efficacy and reluctance to potentially under-treat, due to the irreversible nature of bowel damage that can occur. However, the clinical expert and the product monograph also note that patients should be treated with the lowest effective dose in the interest of safety, and the approach to dosing may vary by the treating physician and severity of disease. All 3 RCTs were placebo-controlled trials, and there is a lack of direct evidence comparing active therapies head-to-head. The 3 RCTs were relatively unique among CD trials in that there was a mandatory taper of corticosteroids, which was considered to be reasonably similar to clinical practice. Overall, the outcomes selected as primary and key secondary outcomes were relevant to decision-making and/or clinical practice, and adequately reflected measures of both efficacies and harms. The duration of follow-up was appropriate for the induction and maintenance phase of treatment. However, when measuring the proportion of patients who experienced events such as hospitalizations or surgeries related to CD, both a 12-week and 52-week time frame were considered to be inadequate to witness a difference between arms, which contributed to uncertainty in interpreting these outcomes. Additionally, the clinical expert noted that endoscopy is not typically conducted at 12 weeks in clinical practice, but rather after 6 to 9 months of initiating treatment due to practical limitations and the invasiveness of the procedure. This logistical limitation was also considered by the expert to be a factor in decision-making around dosing, as patients without symptoms may be experiencing endoscopic activity that would not be seen until the procedure could be completed.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group. Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for

concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: clinical remission per PROs, clinical remission per CDAI, endoscopic response, endoscopic remission, discontinuation of corticosteroid use for CD and CDAI clinical remission in patients taking corticosteroids at induction baseline, endoscopic remission and CDAI clinical remission, change in IBDQ, CR-100, resolution of EIMs among patients who had EIMs at induction baseline, CD-related hospitalization, CD-related surgery, and SAEs.

The induction studies (U-EXCEED and U-EXCEL) were assessed together due to their similarities in population and study design and are reported in Table 3. The maintenance study (U-ENDURE) is reported separately in Table 4 and GRADE assessment was conducted independently for the 2 doses of upadacitinib maintenance therapy (15 mg or 30 mg once daily).

Table 3: Summary of Findings for Upadacitinib Induction Versus Placebo for Patients With Moderately to Severely Active CD and History of Treatment Failure

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Clinical remission				
Proportion of patients with clinical remission per PROs Follow-up: 12 weeks	1,021 (2 RCT)	U-EXCEED: • UPA 45 mg: 398 per 1,000 (95% CI, 345 to 451) • Placebo:140 per 1,000 • Difference: 259 more per 1,000 had remission (95% CI, 187 more to 331 more) U-EXCEL: • UPA 45 mg: 507 per 1,000 (95% CI, 455 to 560) • Placebo: 222 per 1,000 • Difference: 287 more per 1,000 (95% CI, 209 more to 364 more)	High [a]	UPA 45 mg induction results in a clinically important increase in the proportion of patients with clinical remission per PROs at 12 weeks when compared to placebo.
Proportion of patients with clinical remission per CDAIs Follow-up: 12 weeks	1,021 (2 RCT)	U-EXCEED: • UPA 45 mg: 389 more per 1,000 (95% CI, 336 to 442) • Placebo: 211 more per 1,000 • Difference: 179 more per 1,000 had remission (95% CI, 100 more to 258 more) U-EXCEL: • UPA 45 mg: 495 more per 1,000 (95% CI, 442 to 548) • Placebo: 291 more per 1,000 • Difference: 208 more per 1,000 had remission (95% CI, 127 more to 288 more)	Moderate [b]	UPA 45 mg induction likely results in a clinically important increase in the proportion of patients with clinical remission per CDAI at 12 weeks when compared to placebo.
Endoscopic response				
Proportion of patients with endoscopic response Follow-up: 12 weeks	1,021 (2 RCT)	U-EXCEED: • UPA 45 mg: 346 per 1,000 (95% CI, 294 to 398) • Placebo: 35 per 1,000 • Response Rate Difference: 312 more per 1,000 had endoscopic response (95% CI, 255 more to 370 more)	High [c]	UPA 45 mg induction results in a clinically important increase in the proportion with endoscopic response at 12 weeks when compared to placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		U-EXCEL: • UPA 45 mg: 455 per 1,000 (95% CI, 403 to 508) • Placebo: 131 per 1,000 • Difference: 330 more per 1,000 had endoscopic response (95% CI, 262 more to 399 more)		
Endoscopic remission				
Proportion of patients with endoscopic remission Follow-up: 12 weeks	1,021 (2 RCT)	U-EXCEED: • UPA 45 mg: 191 per 1,000 (95% CI, 149 to 234) • Placebo: 23 per 1,000 • Difference: 168 more per 1,000 (95% CI, 120 more to 216 more) U-EXCEL: • UPA 45 mg: 289 per 1,000 (95% CI, 242 to 337) • Placebo: 74 per 1,000 • Difference: 218 more per 1,000 had endoscopic remission (95% CI, 158 more to 278 more)	High [c]	UPA 45 mg induction results in a clinically important increase in the proportion with endoscopic remission at 12 weeks when compared to placebo.
Discontinuation of corticosteroid use and CDAI clinical remission				
Proportion of patients who discontinued corticosteroid use for CD and had clinical remission per CDAI among patients who were receiving corticosteroids at baseline. Follow-up: 12 weeks	358 (2 RCT)	U-EXCEED: • UPA 45 mg: 343 per 1,000 (95% CI, 253 to 432) • Placebo: 117 per 1,000 • Difference: 225 more per 1,000 discontinued corticosteroid use for CD and had clinical remission (95% CI, 111 more to 340 more) U-EXCEL: • UPA 45 mg: 429 per 1,000 (95% CI, 342 to 515) • Placebo: 157 per 1,000 • Difference: 277 more per 1,000 discontinued corticosteroid use for CD and had clinical remission (95% CI, 157 more to 398 more)	Moderate [d]	UPA 45 mg induction likely results in a clinically important increase in the proportion of patients who discontinue corticosteroids for CD and have clinical remission per CDAI (among patients who were receiving corticosteroids at baseline) at 12 weeks compared to placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Endoscopic remission and CDAI clinical remission				
Proportion of patients with endoscopic remission and clinical remission per CDAI Follow-up: 12 weeks	1,021 (2 RCT)	U-EXCEED: • U-EXCEL: •		
HRQoL (IBDQ)				
Change from baseline in IBDQ total score (range of score): 32 (worst HRQoL) to 224 (best HRQoL), LS mean change (95% CI) Follow-up: 12 weeks	848 (2 RCT)	U-EXCEED: • UPA 45 mg: 46.0 points (95% CI, 41.7 to 50.2) • Placebo: 21.6 points • Difference: 24.3 more points change in IBDQ (95% CI, 17.2 more to 31.5 more) U-EXCEL: • UPA 45 mg: 46.3 points (95% CI, 42.5 to 50.0) • Placebo: 24.4 points • Difference: 21.8 more points change in IBDQ (95% CI, 15.6 more to 28.1 more)	High [e]	UPA 45 mg induction results in a clinically important improvement in IBDQ at 12 weeks when compared to placebo.
CR-100				
Proportion with CR-100 Follow-up: 12 weeks	1,021 (2 RCT)	U-EXCEED: • UPA 45 mg: 505 per 1,000 (95% CI, 451 to 560) • Placebo: 275 per 1,000 • Difference: 228 more per 1,000 had CR-100 (95% CI, 144 more to 312 more) U-EXCEL: • UPA 45 mg: 566 per 1,000 (95% CI, 514 to 618) • Placebo: 373 per 1,000 • Difference: 198 more per 1,000 had CR-100 (95% CI, 113 more to 284 more)	High [f]	UPA 45 mg induction results in a clinically important increase in the proportion with CR-100 at 12 weeks when compared to placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Resolution of EIMs				
Proportion with resolution of EIMs among patients who had EIMs at baseline. Follow-up: 12 weeks	420 (2 RCT)	U-EXCEED: • UPA 45 mg: 328 per 1,000 (95% CI, 248 to 409) • Placebo: 217 per 1,000 • Difference: 115 more per 1,000 had resolution of EIMs (95% CI, 15 fewer to 244 more) U-EXCEL: • UPA 45 mg: 285 per 1,000 (95% CI, 213 to 357) • Placebo: 209 per 1,000 • Difference: 90 more per 1,000 had resolution of EIMs (95% CI, 19 fewer to 199 more)	Moderate [g]	UPA 45 mg induction likely results in little to no clinically important difference in the proportion with resolution of EIMs at 12 weeks compared to placebo, among patients who had EIMs at induction baseline.
CD-related hospitalization				
Proportion with CD-related hospitalization Follow-up: 12 weeks	1,021 (2 RCT)	U-EXCEED: • UPA 45 mg: 62 per 1,000 (95% CI, 36 to 88) • Placebo: 88 per 1,000 • Difference: 26 fewer per 1,000 had CD-related hospitalization (95% CI, 76 fewer to 24 more) U-EXCEL: • UPA 45 mg: 37 per 1,000 (95% CI, 17 to 57) • Placebo: 51 per 1,000 • Difference: 14 fewer per 1,000 had CD-related hospitalization (95% CI, 5.2 fewer to 24 more)	Low [h]	UPA 45 mg induction may result in little to no difference in the proportion with CD-related hospitalization at 12 weeks compared to placebo. There is some uncertainty about the clinical importance of the estimates.
CD-related surgery				
Proportion with CD-related surgery Follow-up: 12 weeks	1,021 (2 RCT)	U-EXCEED: •  U-EXCEL: • 		

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
SAEs				
Proportion of patients who experienced any SAE. Follow-up: 12 weeks	1,021 (2 RCT)	U-EXCEED: • UPA 45 mg: 93 per 1,000 (95% CI was not reported) • Placebo: 99 per 1,000 • Difference: 6 fewer per 1,000 had any SAE (95% CI was not reported) U-EXCEL: • UPA 45 mg: 68 per 1,000 (95% CI was not reported) • Placebo: 69 per 1,000 • Difference: 1 fewer per 1,000 had any SAE (95% CI was not reported)	Moderate [i]	UPA 45 mg induction likely results in little to no difference in the proportion with SAEs at 12 weeks compared to placebo. There is some uncertainty about the clinical importance of the estimates.

CD = Crohn disease; CDAI = Crohn Disease Activity Index; CI = confidence interval; CR = clinical response; EIM = extra-intestinal manifestation; HRQoL = health-related quality of life; IBDQ = Inflammatory Bowel Disease Questionnaire; PRO = patient-reported outcome; PY = patient years; RCT = randomized controlled trial; SAE = serious adverse event; UPA = upadacitinib.

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

[a]A difference of 15% between groups was identified by the clinical expert consulted by CADTH as a threshold of clinical importance for this outcome.

[b]Rated down 1 level for serious imprecision as the 95% CI for the between-group difference for each trial crossed the MID of 15% identified by the clinical expert consulted by CADTH for this outcome.

[c]A difference of 5% between groups was identified by the clinical expert consulted by CADTH as a threshold of clinical importance for this outcome.

[d]Rated down 1 level for serious imprecision as the 95% CI for the between-group difference in U-EXCEED trial crossed the threshold of 15% that was identified by the clinical expert consulted by CADTH for this outcome.

[e]A MID of at least 16 points on IBDQ was identified from literature as clinically important. Although the lower boundary of the 95% CI in U-EXCEL was 15.6, this was not considered to be a source of serious imprecision due to its proximity to 16.

[f]A difference of 15% between groups was identified by the clinical expert consulted by CADTH as a threshold of clinical importance for this outcome. Although the lower boundaries of the 95% CIs were below this threshold, given sample size and the proximity of lower bound of the confidence intervals to the estimated threshold across both trials, the imprecision was not considered serious.

[g]Rated down 1 level for serious concern regarding imprecision because the point estimates are below the difference of 15% between groups identified as clinically important by the clinical expert, and the upper bound of the 95% CIs includes the possibility of important benefit.

[h]Rated down 2 levels for serious concerns regarding indirectness and imprecision. Longer-term outcome assessment would be required to compare the effect of treatment more meaningfully on these outcomes. The point estimates are close to null, and the 95% CIs cross null. The clinical experts consulted by CADTH could not provide a threshold of important difference. However, the CADTH review team judged that the effect estimate and confidence interval were unlikely to include any important effect.

[i]Rated down 1 level for serious concerns regarding imprecision. No 95% CI of the difference was available so the optimal information size approach was used to judge imprecision. The clinical experts consulted by CADTH could not provide a threshold of important difference; however, the CADTH review team judged that the effect estimate and the CI were unlikely to include any important effect.

Source: Clinical Study Reports of U-EXCEED and U-EXCEL. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Table 4: Summary of Findings for Upadacitinib Maintenance Versus Placebo for Patients With Moderately to Severely Active CD and History of Treatment Failure

Outcome and follow-up	Dose of UPA	Patients (studies), N	Effect	Certainty	What happens
Clinical remission					
Proportion of patients with clinical remission per PROs Follow-up: 52 weeks	15 mg	334 (1 RCT)	• UPA: 355 per 1,000 (95% CI, 283 to 427) • Placebo: 144 per 1,000 • Difference: 219 more per 1,000 had clinical remission (95% CI, 137 more to 300 more)	Moderate[a]	UPA 15 mg maintenance likely results in a clinically important increase in the proportion of patients with clinical remission per PROs at 52 weeks when compared to placebo.
	30 mg	333 (1 RCT)	• UPA: 464 per 1,000 (95% CI, 389 to 540) • Placebo: 144 per 1,000 • Difference: 318 more per 1,000 had clinical remission (95% CI, 232 more to 403 more)	High[b]	UPA 30 mg maintenance results in a clinically important increase in the proportion of patients with clinical remission per PROs at 12 weeks when compared to placebo.
Proportion of patients with clinical remission per CDAI Follow-up: 52 weeks	15 mg	334 (1 RCT)	• UPA: 373 per 1,000 (95% CI, 300 to 446) • Placebo: 151 per 1,000 • Difference: 237 more per 1,000 had clinical remission (95% CI, 152 more to 321 more)	High[b]	UPA 15 mg maintenance results in a clinically important increase in the proportion of patients with clinical remission per CDAI at 52 weeks when compared to placebo.
	30 mg	333 (1 RCT)	• UPA: 47.6 per 1,000 (95% CI, 401 to 552) • Placebo: 15.1 per 1,000 • Difference: 328 more per 1,000 had clinical remission (95% CI, 239 more to 416 more)	High[b]	UPA 30 mg maintenance results in a clinically important increase in the proportion of patients with clinical remission per CDAI at 52 weeks when compared to placebo.

Outcome and follow-up	Dose of UPA	Patients (studies), N	Effect	Certainty	What happens
Endoscopic response					
Proportion of patients with endoscopic response Follow-up: 52 weeks	15 mg	334 (1 RCT)	• UPA: 276 per 1,000 (95% CI, 208 to 344) • Placebo: 73 per 1,000 • Difference: 210 more per 1,000 had endoscopic response (95% CI, 136 more to more 284)	High[c]	UPA 15 mg maintenance results in a clinically important increase in the proportion of patients with endoscopic response at 52 weeks when compared to placebo.
	30 mg	333 (1 RCT)	• UPA: 401 per 1,000 (95% CI, 327 to 476) • Placebo: 73 per 1,000 • Difference: 337 more per 1,000 had endoscopic response (95% CI, 260 more to 413 more)	High[c]	UPA 30 mg maintenance results in a clinically important increase in the proportion of patients with endoscopic response at 52 weeks when compared to placebo.
Endoscopic Remission					
Proportion of patients with endoscopic remission Follow-up: 52 weeks	15 mg	334 (1 RCT)	• UPA: 191 per 1,000 (95% CI, 131 to 250) • Placebo: 55 per 1,000 • Difference: 144 more per 1,000 had endoscopic remission (95% CI, 77 more to 210 more)	High[c]	UPA 15 mg maintenance results in a clinically important increase in the proportion of patients with endoscopic remission at 52 weeks when compared to placebo.
	30 mg	333 (1 RCT)	• UPA: 286 per 1,000 (95% CI, 218 to 355) • Placebo: 55 per 1,000 • Difference: 236 more per 1,000 had endoscopic remission (161 more to 310 more)	High[c]	UPA 30 mg maintenance results in a clinically important increase in the proportion of patients with endoscopic remission at 52 weeks when compared to placebo.

Outcome and follow-up	Dose of UPA	Patients (studies), N	Effect	Certainty	What happens
Discontinuation of corticosteroid use and CDAI clinical remission					
Proportion of patients who discontinued corticosteroid use for CD for at least 90 days at week 52 and had clinical remission per CDAI among patients who were receiving corticosteroids at induction baseline. Follow-up: 52 weeks	15 mg	124 (1 RCT)	• UPA: 397 per 1,000 (95% CI, 276 to 518) • Placebo: 49 per 1,000 • Difference: 354 more per 1,000 discontinued corticosteroid use for CD and had clinical remission (95% CI, 233 more to 475 more)	Moderate[d]	UPA 15 mg maintenance likely results in a clinically important increase in the proportion of patients who discontinue corticosteroids for CD and have clinical remission per CDAI (among patients who were receiving corticosteroids at induction baseline) at 52 weeks compared to placebo.
	30 mg	124 (1 RCT)	• UPA: 397 per 1,000 (95% CI, 276 to 518) • Placebo: 49 per 1,000 • Difference: 323 more per 1,000 discontinued corticosteroid use for CD and had clinical remission (95% CI, 201 more to 445 more)	Moderate[d]	UPA 30 mg likely maintenance results in a clinically important increase in the proportion of patients who discontinue corticosteroids for CD and have clinical remission per CDAI (among patients who were receiving corticosteroids at induction baseline) at 52 weeks compared to placebo.
Endoscopic remission and CDAI clinical remission					
Proportion of patients with endoscopic remission and clinical remission per	15 mg	334 (1 RCT)	• UPA: 148 per 1,000 (95% CI, 95 to 202) • Placebo: 37 per 1,000 • Difference: 122 more per 1,000 had both endoscopic and clinical remission (95% CI, 63 more to 181 more)	High[c]	UPA 15 mg maintenance results in a clinically important increase in the proportion of patients with both endoscopic and clinical remission (per CDAI) at 52

Outcome and follow-up	Dose of UPA	Patients (studies), N	Effect	Certainty	What happens
CDAI Follow-up: 52 weeks					weeks when compared to placebo.
	30 mg	333 (1 RCT)	• UPA: 232 per 1,000 (95% CI, 168 to 296) • Placebo: 37 per 1,000 • Difference: 19.8 more per 1,000 had both endoscopic and clinical remission (95% CI, 130 more to 266 more)	High[c]	UPA 30 mg maintenance results in a clinically important increase in the proportion of patients with both endoscopic and clinical remission (per CDAI) at 52 weeks when compared to placebo.
HRQoL (IBDQ)					
Change from baseline in IBDQ total score (range of score: 32 (worst HRQoL) to 224 (best HRQoL)), LS mean change. Follow-up: 52 weeks	15 mg	119 (1 RCT)	• UPA: 59.3 points (95% CI, 52.9 to 65.6) • Placebo: 46.4 points • Difference: 12.9 more points on IBDQ (95% CI, 4.3 to 21.4)	Moderate[e]	UPA 15 mg maintenance likely results in little to no difference in IBDQ at 52 weeks when compared with placebo.
	30 mg	135 (1 RCT)	• UPA: 64.5 points (95% CI, 58.3 to 70.7) • Placebo: 46.4 points • Difference: 18.1 more points on IBDQ (95% CI, 9.8 to 26.4)	Moderate[f]	UPA 30 mg maintenance likely results in a clinically important improvement in IBDQ at 52 weeks when compared with placebo.
CR-100					
Proportion with CR-100 Follow-up: 52 weeks	15 mg	334 (1 RCT)	• UPA: 414 per 1,000 (95% CI, 340 to 488) • Placebo: 152 per 1,000 • Difference: 271 more per 1,000 had CR-100 (95% CI, 183 more to 358 more)	High[c]	UPA 15 mg maintenance results in a clinically important increase in the proportion of patients with CR-100 at 52 weeks when compared with placebo.

Outcome and follow-up	Dose of UPA	Patients (studies), N	Effect	Certainty	What happens
	30 mg	333 (1 RCT)	• UPA: 512 per 1,000 (95% CI, 436 to 587) • Placebo: 152 per 1,000 • Difference: 364 more per 1,000 had CR-100 (95% CI, 275 to 452)	High[c]	UPA 30 mg maintenance results in a clinically important increase in the proportion of patients with CR-100 at 52 weeks when compared with placebo.
Resolution of EIMs					
Proportion with resolution of EIMs among patients who had EIMs at baseline. Follow-up: 52 weeks	15 mg	127 (1 RCT)	• UPA: 246 per 1,000 (95% CI, 138 to 354) • Placebo: 152 per 1,000 • Difference: 96 more per 1,000 had resolution of EIMs (95% CI, 34 fewer to 226 more)	Low[g]	UPA 15 mg maintenance may result in little to no clinically important increase in the proportion of patients with resolution of EIMs at 52 weeks when compared with placebo, among patients who had EIMs at induction baseline.
	30 mg	139 (1 RCT)	• UPA: 356 per 1,000 (95% CI, 246 to 466) • Placebo: 152 per 1,000 • Difference: 220 more per 1,000 had resolution of EIMs (95% CI, 93 more to 348 more)	Moderate[h]	UPA 30 mg maintenance likely results in a clinically important increase in the proportion of patients with resolution of EIMs at 52 weeks when compared with placebo, among patients who had EIMs at induction baseline.
CD-Related Hospitalization – Maintenance					
Proportion with of CD-related hospitalization Follow-up: 52 weeks	15 mg	334 (1 RCT)	• UPA: 112 per 1,000 (95% CI, 51 to 173) • Placebo: 120 per 1,000 • Difference: 8 fewer per 1,000 had CD-related hospitalization (104 fewer to 88 more)	Low[i]	UPA 15 mg maintenance may result in little to no difference in CD-related hospitalizations at 52 weeks compared to placebo. There is some

Outcome and follow-up	Dose of UPA	Patients (studies), N	Effect	Certainty	What happens
					uncertainty about the clinical importance of the estimates.
	30 mg	333 (1 RCT)	• UPA: 78 per 1,000 (95% CI, 29 to 126) • Placebo: 120 per 1,000 • Difference: 42 fewer per 1,000 had CD-related hospitalization (95% CI, 131 fewer to 47 more)	Low[i]	UPA 30 mg maintenance may result in little to no difference in CD-related hospitalizations at 52 weeks compared to placebo. There is some uncertainty about the clinical importance of the estimates.
CD-Related Surgery – Maintenance					
Incidence rate (n/100 PY) of CD-related surgery Follow-up: 52 weeks	15 mg	334 (1 RCT)	•		
	30 mg	333 (1 RCT)	•		
SAEs – Maintenance					
Proportion of patients who experienced any SAE. Follow-up: 52 weeks	15 mg	452 (1 RCT)	• UPA: 118 per 1,000 (95% CI was not reported) • Placebo: 139 per 1,000 • Difference: 21 fewer per 1,000 had any SAE (95% CI was not reported)	Moderate[j]	UPA 15 mg maintenance likely results in little to no difference in SAEs at 52 weeks compared to placebo. There is some uncertainty about the clinical importance of the estimates.

Outcome and follow-up	Dose of UPA	Patients (studies), N	Effect	Certainty	What happens
	30 mg	450 (1 RCT)	• UPA: 105 per 1,000 (95% CI was not reported) • Placebo: 139 per 1,000 • Difference: 34 fewer per 1,000 had any SAE (95% CI was not reported)	Moderate[j]	UPA 30 mg maintenance likely results in little to no difference in SAEs at 52 weeks compared to placebo. There is some uncertainty about the clinical importance of the estimates.

CD = Crohn disease; CDAI = Crohn Disease Activity Index; CI = confidence interval; CR = clinical response; EIM = extra-intestinal manifestation; HRQoL = health-related quality of life; IBDQ = Inflammatory Bowel Disease Questionnaire; PRO = patient-reported outcome; PY = patient years; RCT = randomized controlled trial; SAE = serious adverse event; UPA = upadacitinib.

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

[a]Rated down 1 level for serious imprecision as the 95% CI of each trial crossed the difference of 15% between groups identified by the clinical expert consulted by CADTH as clinically important for this outcome.

[b]A difference of 15% between groups was identified by the clinical expert consulted by CADTH as a threshold of clinical importance for this outcome.

[c]A difference of 5% between groups was identified by the clinical expert consulted by CADTH as a threshold of clinical importance for this outcome.

[d]Rated down 1 level for serious concerns regarding imprecision. No 95% CI of the difference was available so the optimal information size approach was used to judge imprecision. There is no established MID.

[e]Rated down 1 levels for serious concern regarding imprecision because the point estimate was lower than the literature-reported MID of ≥ 16 points on the IBDQ and the 95% CI crossed the MID.

[f]Rated down 1 level for serious concern regarding imprecision because the 95% CI crossed the literature-reported MID of ≥ 16 points on the IBDQ.

[g]Rated down 2 levels for very serious concerns regarding imprecision because the point estimate was lower than the difference of 15% between groups identified by the clinical expert consulted by CADTH as clinically important for this outcome, and the 95% CI crossed the clinical importance threshold.

[h]Rated down 1 level for serious concerns regarding imprecision because and the 95% CI crossed the difference of 15% between groups identified by the clinical expert consulted by CADTH as clinically important for this outcome.

[i]Rated down 2 levels for serious concerns regarding indirectness and imprecision. Longer-term outcome assessment would be required to compare the effect of treatment more meaningfully on these outcomes. The point estimates are close to null and the 95% CIs cross null. These outcomes may not have been tested for multiplicity in the trial and should be considered as supportive evidence. The clinical experts consulted by CADTH could not provide a threshold of important difference, however the CADTH review team judged that the effect estimate and confidence interval were unlikely to include any important effect.

[j]Rated down 1 level for serious concern regarding imprecision. No 95% CI of the difference was available. There is no established MID so the optimal information size approach was used. The clinical experts consulted by CADTH could not provide a threshold of important difference, however the CADTH review team judged that the effect estimate and confidence interval were unlikely to include any important effect.

Source: Clinical Study Reports of U-ENDURE. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Indirect Comparisons

One indirect treatment comparison (ITC) was submitted by the sponsor to estimate the relative efficacy and safety of upadacitinib versus advanced therapies for the treatment of adult patients with moderately to severely active CD.

Description of Studies

Studies included in the ITC enrolled adult and adolescent patients with moderately to severely active CD and advanced treatments for CD, namely upadacitinib, vedolizumab (VDZ), ustekinumab (UST), risankizumab (RZB), adalimumab (ADA), and infliximab (IFX). Efficacy outcomes included clinical outcomes (remission and response), endoscopic outcomes (remission and response), and safety outcomes (any AE, SAE, serious infection, and AEs leading to discontinuation), which generally aligned with the outcomes that were important to patients and clinicians.

Efficacy Results

[redacted]

Harms Results

[redacted]

Critical Appraisal

[redacted]

Economic Evidence

Table 5: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Decision-tree followed by a Markov model
Target population	Patients with moderately to severely active CD with an inadequate response to, loss of response to, or intolerance to conventional care (CCF subgroup) or biologic therapy BF subgroup).
Treatments	Upadacitinib: 45 mg for induction + 15 mg for maintenance (UPA 15) Upadacitinib: 45 mg for induction + 30 mg for maintenance (UPA 30)
Dose regimen	45 mg once daily for 12 weeks, followed by 15 mg or 30 mg once daily
Submitted price	Upadacitinib, 15 mg: $51.68 per tablet Upadacitinib, 30 mg: $76.96 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 $51.68, $76.96, and $101.81 per 15 mg, 30 mg, and 45 mg tablet, respectively, the annual cost of upadacitinib is $23,074 for year 1 and $18,876 thereafter. Assuming the highest maintenance dose (30 mg), the annual cost of upadacitinib is $30,178 for year 1 and $28,090 thereafter.
Comparators	• Adalimumab biosimilar • Infliximab biosimilar • Vedolizumab • Ustekinumab • Conventional care (weighted basket of corticosteroids, aminosalicylates, immunomodulators) • Risankizumab (included in scenario analysis)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (60 years)
Key data sources	Network meta-analyses; effectiveness of upadacitinib informed by U-EXCEED, U-EXCEL and U-ENDURE
Key limitations	• The comparative efficacy and safety of upadacitinib relative to other advanced treatments are uncertain owing to a lack of head-to-head trials and [redacted] Indirect evidence submitted by the sponsor suggests [redacted] compared to other advanced treatments for the treatment of moderately to severely active CD. • The long-term efficacy of upadacitinib is uncertain owing to a lack of clinical data beyond 52 weeks. Potential waning of effectiveness was not explored. • The sponsor's model did not differentiate between causes of surgery, types of surgery, and does not account for the impacts of surgery and surgical complications on quality of life, risk of recurrence, and future complications.
CADTH reanalysis results	• Given the limitations identified within the sponsor's economic analysis, CADTH was unable to provide a more reliable estimate of the cost-effectiveness of upadacitinib. Based on the sponsor's analysis, upadacitinib is not a cost-effective treatment option for moderately to severely active CD in either the CCF or BF subgroup at a willingness to pay threshold of $50,000 per QALY gained. The probability of upadacitinib being the optimal treatment was less than 1% in all subgroups.

Component	Description
	• There is insufficient clinical evidence to justify a price premium for upadacitinib over currently available biologic treatments for moderately to severely active CD in either the CCF or BF subgroup. To ensure cost-effectiveness, UPA should be priced no more than the lowest-cost biologic used to manage moderately to severely CD that is funded.

BF = biologic failure; CCF = conventional care failure; CD = Crohn disease; QALY= quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitation with the sponsor's analysis: market size was estimated using a claims-based approach, which was not specific to the Health Canada-indicated population (i.e., moderately to severely active CD and prior failure of at least 1 conventional or biologic treatment). Using a claims-based approach to estimate the number of eligible patients introduces uncertainty with the anticipated budget impact of upadacitinib that could not be resolved. Additional limitations include uncertainty in the proportion of patients eligible for public drug plan coverage, the omission of risankizumab as a comparator in the sponsor's base case, uncertainty in the annual cost of UPA, uncertainty in the market uptake of upadacitinib, and the presence of confidential prices for most comparators. Without more reliable input values to estimate the eligible population size, the sponsor's base case was maintained.

The net budget impact of reimbursing upadacitinib for the treatment of moderate to severe CD among patients with a prior treatment failure was estimated by the sponsor to be $7,325,987 in year 1, $20,226,831 in year 2, and $39,587,222 in year 3. The net budget impact over the 3-year time horizon was $67,140,041.

CDEC Information

Members of the Committee

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

Meeting date: October 25, 2023

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

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