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CADTH Reimbursement Recommendation

Upadacitinib (Rinvoq)

Indication: For the treatment of adults and adolescents 12 years of age and older with refractory moderate to severe atopic dermatitis who are not adequately controlled with a systemic treatment (e.g., steroid or biologic) or when use of those therapies is inadvisable. Upadacitinib can be used with or without topical corticosteroids

Sponsor: AbbVie Corporation

Recommendation: Reimburse with conditions

CADTH

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

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

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Rinvoq?

CADTH recommends that Rinvoq be reimbursed by public drug plans for the treatment of adults and adolescents 12 years of age and older with refractory moderate to severe atopic dermatitis (AD) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Rinvoq should only be covered to treat patients who have previously tried and are refractory to, or who are ineligible or cannot tolerate, the highest tolerated dose of topical treatments for AD combined with phototherapy (where available), and at least 1 of methotrexate, cyclosporine, mycophenolate mofetil, or azathioprine.

What Are the Conditions for Reimbursement?

Rinvoq should only be reimbursed if prescribed by a dermatologist, allergist, clinical immunologist, or pediatrician, and the cost of Rinvoq is reduced.

Why Did CADTH Make This Recommendation?

- In 4 clinical trials, treatment with Rinvoq reduced AD severity and symptoms compared to treatment with placebo.
- Rinvoq may meet some of the needs that are important to patients, including reducing AD severity and symptoms and improving health-related quality of life.
- Based on CADTH's assessment of the health economic evidence, Rinvoq may not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Rinvoq compared with dupilumab over the duration of treatment.
- Based on public list prices, Rinvoq is estimated to save the public drug plans approximately $62 million over the next 3 years.

Additional Information

What is Atopic Dermatitis?

AD is a condition that affects the skin. People with AD have dry, red skin that is extremely itchy. Constant scratching can cause the skin to split and bleed, which can cause skin infections. Oozing and weeping sores can also occur in more severe forms of AD. Severe dermatitis can be physically disabling or incapacitating and cause anxiety or depression. The lifetime prevalence of AD is estimated to be up to 17% in the Canadian population.

Unmet Needs in Atopic Dermatitis

There is no cure for AD, and treatment aims to provide symptom relief and control symptoms in the longer term. Although many treatments are approved in Canada to treat AD, symptoms may not be controlled with existing drugs in some patients. Other treatment options are needed for these patients.

How Much Does Rinvoq Cost?

Treatment with Rinvoq 15 mg is expected to cost approximately $17,768 per year. The 30 mg dose is expected to cost approximately $27,010 per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that upadacitinib be reimbursed for the treatment of adults and adolescents 12 years of age and older with refractory moderate to severe AD who are not adequately controlled with a systemic treatment (e.g., steroid or biologic) or when use of those therapies is inadvisable only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Four clinical studies evaluated the use of upadacitinib in patients with moderate to severe chronic AD and inadequate response to topical or systemic treatments. Three double-blind, placebo-controlled studies (Measure Up 1 [n = 847], Measure Up 2 [n = 836], and AD Up [n = 901]) in adults and adolescents (≥ 40 kg) demonstrated that upadacitinib 15 mg and 30 mg improved disease severity based on the Eczema Area and Severity Index (EASI) 75 score (i.e., a 75% or greater improvement from baseline in the EASI score) and the validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) scores index when compared to placebo. Disease severity was improved whether upadacitinib was used as monotherapy (Measure Up 1 and 2 studies) or in addition to topical corticosteroids (AD Up study). The evidence from these studies also indicates that upadacitinib (15 mg and 30 mg) is likely to reduce AD symptoms (as assessed by the pruritus numeric rating scale [NRS], patient oriented eczema measure [POEM], and atopic dermatitis [ADerm] Impact Scale), improve health-related quality of life [HRQoL] (through the dermatology life quality index [DLQI]), and mood and productivity domains (hospital anxiety and depression scale and the work productivity and activity index). One comparative study (Heads Up, n = 692) demonstrated superior efficacy of upadacitinib 30 mg in reducing disease severity and symptoms (based on the EASI 75 and pruritus NRS) when compared to dupilumab 300 mg at week 16; however, after 24 weeks this difference was no longer observed. In all 4 studies, the subgroup of patients who previously used systemic therapies (e.g., steroid or biologic) showed similar results to the overall study populations for the primary end points of response based on the EASI 75 at week 16, and the vIGA-AD (except for the Heads Up study where no vIGA-AD was assessed). The subgroup analysis of patients who previously used systemic therapies was not defined a priori and may be underpowered; as a result, there was uncertainty about the generalizability of the results from the included studies to the approved indication. In addition, there was no evidence for dose escalation to 30 mg once daily in patients with an inadequate response to upadacitinib 15 mg once daily, and there was no clinical evidence for dose de-escalation to 15 mg once daily in patients with adequate response on upadacitinib 30 mg once daily.

Patients identified a need for new AD treatment alternatives that are effective in reducing pruritus, pain, flares, and rashes, and improving sleep and HRQoL. CDEC concluded that the evidence for upadacitinib appears to address some of these outcomes.

Due to the lack of evidence evaluating dose escalation, de-escalation, and the proportions of patients taking either 15 mg or 30 mg at any time, the cost-effectiveness of upadacitinib is unable to be determined for the dosing strategy approved by Health Canada. CADTH exploratory cost-effectiveness estimates are highly uncertain, biased in favour of upadacitinib, and highly sensitive to assumptions about the price of both upadacitinib and dupilumab.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients must have had an adequate trial (with a documented refractory disease), or were intolerant (with documented intolerance), or are ineligible for each of the following therapies: 1.1. maximally tolerated medical topical therapies for AD combined with phototherapy (where available), and 1.2. maximally tolerated medical topical therapies for AD combined with at least 1 of the 4 systemic immunomodulators (methotrexate, cyclosporine, mycophenolate mofetil, or azathioprine).	Conventional approaches to moderate to severe AD refractory to topical therapies have, for a number of years, included older immunomodulatory drugs. Concerns about their long-term safety continue; however, clinical experience with systemic immunomodulators is extensive and the costs are modest compared to novel drugs. CDEC accepted the opinion of the clinical expert and assessments of practice in other jurisdictions and considered that at least 1 conventional immunomodulatory drug be attempted before upadacitinib is used for refractory AD, particularly as information about the long-term safety of the latter is awaited. In addition, the majority of patients enrolled in the trials reviewed by CDEC had a prior exposure to at least 1 systemic therapy for AD, where the percentage of patients with prior exposure to at least 1 systemic treatment for AD in the included trials were: 46.4%, in Measure Up 1, 54.5% in Measure Up 2, 66.6% in AD Up, and 51.0% in Heads Up.	1. Phototherapy may not be available in all jurisdictions. Geographic inability to access phototherapy should not preclude patients from accessing upadacitinib if otherwise indicated. 2. Adequate control and refractory disease are optimally defined using similar criteria to those used in the upadacitinib trials, such as achieving EASI 75. 3. The clinical expert noted that an "adequate trial" for patients with AD who undergo therapy with phototherapy, methotrexate, cyclosporine, mycophenolate mofetil, and azathioprine is defined as follows: 3.1. For phototherapy: the typical duration would be considered 12 weeks (3 times per week) 3.2. For methotrexate: an adequate trial would be 10 mg to 20 mg per week for 12 weeks 3.3. For cyclosporine: an adequate trial would be 2.5 mg/kg to 5 mg/kg per day for 12 weeks 3.4. For mycophenolate mofetil: an adequate trial would be 1 g twice daily for 12 weeks 3.5. For azathioprine: an adequate trial would be 1.5 to 2.5 mg/kg/day for 12 weeks.

Reimbursement condition	Reason	Implementation guidance
2. The physician must provide the EASI score and vIGA-AD score at the time of initial request for reimbursement.	The Measure Up 1, Measure Up 2, AD Up, and Heads Up studies enrolled patients with an EASI score of 16 points or higher, and a vIGA-AD score of 3 or higher.	—
Renewal		
3. The maximum duration of initial authorization is 20 weeks. For renewal after initial authorization, the physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as a 75% or greater improvement from baseline in the EASI score (EASI 75) 20 weeks after treatment initiation.	CDEC has recommended that the first renewal assessment for upadacitinib occur after 16 to 20 weeks of treatment based on the timing of the primary end point evaluation in the pivotal studies (i.e., EASI 75 at 16 weeks) with 4 weeks of additional flexibility to accommodate scheduling of follow-up evaluations. The clinical expert noted to CDEC that in clinical practice, the response to treatment is assessed 16 to 20 weeks after initiating upadacitinib, then every 6 months thereafter.	—
4. For subsequent renewal, the physician must provide proof of maintenance of EASI 75 response from baseline every 6 months for subsequent authorizations.		—
Prescribing		
5. The patient must be under the care of a dermatologist, allergist, clinical immunologist, or pediatrician who has expertise in the management of moderate to severe AD.	Accurate diagnosis and follow-up of patients with refractory moderate to severe AD is important to ensure that upadacitinib is prescribed to the most appropriate patients. In addition, there are several treatment options that may be considered when selecting the most appropriate therapy for patients, which is best determined by dermatologists, allergists, clinical immunologists, or pediatricians who have expertise in the management of moderate to severe AD, and who are familiar with this treatment paradigm.	—
6. Upadacitinib should not be used in combination with phototherapy, any immunomodulatory drugs (including biologics) or other JAK inhibitor treatment for moderate to severe AD.	There is no evidence to demonstrate a beneficial effect of upadacitinib when used in combination with phototherapy, any immunomodulatory drugs (including biologics), or other JAK inhibitor treatment for moderate to severe AD.	—
Pricing		
7. A reduction in price	The cost-effectiveness of upadacitinib, when administered according to the Health Canada–recommended dosing strategy, is unknown. In an exploratory analysis, no price reduction was necessary for upadacitinib 15 mg to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY compared to BSC. Exploratory	—

Reimbursement condition	Reason	Implementation guidance
	analysis suggested that a price reduction of 35% would be needed for upadacitinib 30 mg to be considered cost-effective compared to upadacitinib 15 mg. Exploratory analysis was performed using the manufacturer's submitted drug price for upadacitinib and publicly available prices for comparators.	

AD = atopic dermatitis; BSC = best supportive care; CDEC = Canadian Drug Expert Committee; EASI = Eczema Area and Severity Index; JAK = Janus kinase; QALY = quality-adjusted life-year; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis.

Discussion Points

- In all 4 studies reviewed by CDEC, the subgroup of patients who previously used systemic therapies showed similar results to the overall study populations for the primary end points of response based on the EASI 75 at week 16, and the vIGA-AD (except for the Heads Up study where no vIGA-AD was assessed). CDEC discussed that while this implies that the beneficial effect of upadacitinib in the population previously treated with systemic therapies reflects the overall study populations, the results from the subgroup analyses should be interpreted with caution because the subgroup analyses were not prespecified in the studies. The clinical expert noted that the response to upadacitinib would likely be similar for those with and without prior exposure to systemic therapy for AD.
- CDEC noted that based on the trials, moderate to severe AD is defined as an EASI score of 16 points or higher, and a vIGA-AD score of 3 or higher.
- The clinical expert noted to CDEC that in clinical practice, medical topical therapies would continue to be used in combination with upadacitinib.
- One indirect treatment comparison (ITC) compared upadacitinib with dupilumab in adults or adolescents with moderate to severe AD with an inadequate response to cyclosporine. This ITC suggested that [redacted]. However, a conclusion regarding the long-term efficacy of upadacitinib compared to dupilumab cannot be drawn as the ITC used study results collected over a relatively short duration when contextualized to the chronic nature of AD. There is also uncertainty due to the inherent heterogeneity across trials in the networks.
- CDEC discussed that the duration of the 4 studies reviewed is not adequate to assess the long-term efficacy and safety of upadacitinib.
- CDEC considered exploratory analyses conducted by CADTH, which considered upadacitinib 15 mg and upadacitinib 30 mg separately (i.e., not the recommended dosing strategy). In these scenario analyses, upadacitinib 15 mg was associated with an incremental cost-effectiveness ratio (ICER) of $48,616 per quality-adjusted life-year gained compared with best supportive care, while upadacitinib 30 mg plus topical corticosteroids (TCS) was associated with an ICER of $372,226 per quality-adjusted life-year gained compared with upadacitinib 15 mg plus TCS. Exploratory analyses remain subject to the limitations identified within the CADTH Pharmacoeconomic Report.
- The presence of an assessment time bias and a lack of direct comparative evidence for the Health Canada–approved population adds considerable uncertainty to incremental effectiveness comparisons between upadacitinib and dupilumab. Cost-effectiveness

analyses were performed using public list prices for all treatments, including dupilumab. The estimated incremental cost of upadacitinib versus dupilumab is therefore also uncertain, given that the negotiated price that drug plans pay for dupilumab is likely lower than the list price. In CADTH exploratory analysis, cost-effectiveness was highly sensitive to changes in dupilumab price. Price negotiations for upadacitinib should reflect this uncertainty in both incremental cost and incremental effectiveness.

Background

AD (also known as atopic eczema) is an inflammatory, chronic skin disease affecting 20% of children and 2% to 8% of adults worldwide. In Canada, the lifetime prevalence of AD is up to 17% of the population. AD is characterized by severe pruritus, rash, and scratching. Secondary skin infections are common. AD usually develops before the age of 5 and may persist into adulthood. Symptoms can worsen through the night, resulting in sleep loss and affecting school or work activities, and HRQoL is also altered. The goals of AD treatments are to manage and prevent flares. The treatments include general skin care and topical anti-inflammatory medication (TCS). If these methods fail, patients may use off-label systemic therapy (i.e., immunosuppressant therapy) or phototherapy. Other options include topical calcineurin inhibitors (pimecrolimus and tacrolimus) and crisaborole. Systemic therapy involves antimicrobials, antihistamines, or immunomodulators — including methotrexate, cyclosporine, mycophenolate mofetil, and azathioprine. These commonly used off-label treatments are administered in the lowest dose and for the shortest duration possible due to the possibility of side effects. Dupilumab is used to treat patients with moderate to severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Upadacitinib is a small molecule, reversible, Janus kinase inhibitor indicated for the treatment of adults and adolescents 12 years of age and older with refractory moderate to severe AD who are not adequately controlled with a systemic treatment (e.g., steroid or biologic) or when use of those therapies is inadvisable. Upadacitinib can be used with or without TCS. The product monograph for upadacitinib contains black box warnings regarding the risk of serious infections, malignancies, and thrombosis. It is recommended that treatment with upadacitinib be interrupted if a patient develops a serious infection until the infection is controlled. Upadacitinib is available as 15 mg or 30 mg oral extended-release tablets. The Health Canada–recommended starting dose of upadacitinib for adult patients is 15 mg once daily. If an adequate response (e.g., EASI 75) is not achieved, an increase can be considered to 30 mg once daily. For some patients, such as those with severe disease, a starting dose of 30 mg once daily may be appropriate. Upadacitinib should be discontinued if an adequate response is not achieved with the 30 mg dose after 16 weeks of treatment. In adolescents 12 to 17 years of age, the recommended dose is 15 mg once daily. Upadacitinib has not been studied in adolescents weighing less than 40 kg.

Sources of Information Used by the Committee

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

- a review of 4 randomized studies (3 double-blind, placebo-controlled studies and 1 double-blind, double-dummy, active controlled study) in patients with moderate to severe AD
- patients perspectives gathered by 3 patient groups, the Eczema Society of Canada (ESC), the Canadian Skin Patient Alliance (CSPA), and Eczéma Québec — the last 2 provided a joint submission of input from public drug plans and cancer agencies that participate in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with AD
- input from 1 clinician group, The Atlantic Specialist Group Managing Atopic Dermatitis
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Three patient groups responded to CADTH's call for patient input: the ESC, and the CSPA and Eczéma Québec, who provided a joint submission. ESC is a registered Canadian charity dedicated to improving the lives of people in Canada living with eczema with a mission of support, education, awareness, and research. CSPA is a national non-profit organization advocating, educating, and supporting people living in Canada who are impacted by skin, hair, and nail disorders. Eczéma Québec is a patient advisory committee and registered non-profit organization.

ESC gathered survey data from more than 3,000 adults living with AD and the caregivers of children living with AD. Meanwhile, Eczéma Québec and CSPA developed and circulated a web-based survey that was distributed through both organizations' newsletter and social media. There were 56 respondents to the survey.

The patient groups reported that AD negatively impacts the patient and their family and can lead to psychological distress. Patients frequently report that itch is the most burdensome symptom of AD, and more than half of adult respondents with severe AD reported rarely being able to control their urge to scratch. Itch also significantly impacts sleep; patients report being woken frequently and having trouble falling and staying asleep due to their itch. The severity of AD correlates with impacts on HRQoL as well as lost productivity at school and burden on health systems. AD also has significant impacts in terms of the psychosocial burden of symptoms. All respondents experienced itching because of their condition. According to the CSPA survey, other symptoms included redness of the skin (87.88%), repeated rashes (84.85%), frequent scratching (84.85%), cracked skin (84.85%), dry and rough skin (78.79%), disrupted sleep (75.76%), bleeding (69.70%), flaking of the skin (69.70%), pain (69.70%), thickening of the skin (60.61%), oozing (48.48%), swelling (42.42%), lichenification (39.39%), and blistering (36.36%). From the ESC survey, 32% of adult respondents with moderate or severe AD have missed work events due to their condition, and 30% have had to change careers or give up certain activities. Caregivers noted that AD places a significant emotional toll on the entire family, and feelings of guilt, frustration, anger, and sadness are common. A total of 41% of caregivers reported they feel like a failure when they cannot control their child's flares. Patients and caregivers reported that the mental health impact of AD is a significant aspect of the condition and is often not understood by others, nor prioritized by health care

providers. Uncontrolled chronic AD can lead to feelings of depression and anxiety as well as poor self-esteem, low energy, and, sadly, in some extreme cases, suicidal thoughts.

Most patients expressed their dissatisfaction with the treatment options currently available to them. Another source of frustration for these participants was that they didn't see these treatments as long-term options but rather "temporary." Respondents also expressed concern over the financial impact of treatments.

Patients believe that the need for more treatment options for uncontrolled AD is critical. Overall, patients desire improvement in managing the itch, reducing flares and rashes, improved quality of life, and improved sleep. Patients also want to improve the appearance of their hands and eyes, less apparent eczema, and to obtain pain relief.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

The clinical expert consulted by CADTH visualized the ideal treatment for AD as one that is available to all Canadians, is cost-effective in the context of a publicly funded health care system, has a proven long-term safety record, and completely reverses the barrier dysfunction and immunologic abnormalities that constitute AD.

Upadacitinib was considered by the clinical expert as a potentially useful addition to the currently available therapeutic options for AD. Especially in patients who have contraindications to, experience adverse effects from, or who are unresponsive to off-label immunosuppressive drugs. Upadacitinib could also be of value in patients treated with dupilumab who have a suboptimal response, who develop severe conjunctivitis or other ocular side effects from dupilumab, or are intolerant to injections (e.g., due to severe injection site reactions) and prefer an oral drug. Furthermore, the clinical expert noted that all patients with AD treated with upadacitinib would be expected to continue on with emollients, TCS, and/or topical calcineurin inhibitors.

According to the clinical expert, upadacitinib can be another effective treatment option in the Canadian clinical landscape. Off-label immunosuppressives or dupilumab are not expected to be used in combination with upadacitinib; however, the clinical expert believed that many practitioners would still consider a trial of methotrexate and cyclosporine before initiating treatment with upadacitinib. The clinical expert suggested that patients less suitable for treatment with upadacitinib would be those with AD who are well controlled with topical therapy, phototherapy, and/or intermittent off-label immunosuppressive therapy, as well as patients well controlled with dupilumab. Upadacitinib should be avoided in patients with potential contraindications to Janus kinase inhibitors such as severe active infections; malignancy, including ongoing treatment with chemotherapy (including checkpoint inhibitors); severe hepatic disease; severe renal disease; pregnancy or lactation; history of thromboembolic events; and pre-existing hematologic disease, as well as patients weighing less than 40 kg.

In general, the outcomes used in clinical practice are aligned with the outcomes typically used in clinical trials of AD treatments. Of these outcome measurements, a rational benchmark was the response of 75% reduction in EASI score from baseline values at 16 weeks. In the opinion of the clinical expert, patients placed on upadacitinib would be re-evaluated at 16 weeks after initiating treatment. Those who are judged to be responders at this visit would be

seen subsequently at 6-month intervals. Those who have not reached response targets at 16 weeks would be re-evaluated at 20 weeks following initiation of drug.

According to the clinical expert, patients deemed to have severe symptoms would start on the 30 mg for 16 weeks dose and would get an assessment for response (e.g., EASI 75); if a response is reached, they would switch to the 15 mg dose. The product monograph approved by Health Canada states that patients who are receiving 15 mg and do not achieve a response after 16 weeks of treatment would be switched to the 30 mg dose. The product monograph also states that if patients do not achieve adequate response (e.g., EASI 75) after 16 weeks of treatment on the 30 mg dose, upadacitinib should be discontinued.

The factors anticipated by the clinical expert to be used as criteria for discontinuation included failure to achieve clinically meaningful response at 16 to 20 weeks, failure to maintain an adequate response on long-term maintenance, development of a hypersensitivity response judged to be due to upadacitinib, treatment-emergent adverse effects (e.g., lymphopenia, neutropenia, arterial thrombosis, venous thromboembolism), and treatment-emergent severe infections or malignancies.

There are no special challenges for the administration of the drug. However, a specialist would still be required to diagnose, treat, and monitor patients taking upadacitinib. Appropriate specialists will include pediatric dermatologists, general dermatologists, or pediatricians with experience in treating patients with AD. Dermatologists are well-versed in appropriate dosing and duration of therapy and appropriate monitoring for potential toxicities.

Clinician Group Input

One clinician group provided input on the reimbursement review of upadacitinib for the treatment of adult and adolescents with moderate to severe AD: The Atlantic Specialist Group Managing Atopic Dermatitis is a group of physicians, including general practitioners, dermatology, and allergy and immunology specialists managing patients with AD. The members of the group are located in various clinical settings across Atlantic Canada.

The clinician group indicated that the greatest unmet need is in the subset of patients with moderate to severe AD, in which the main unmet need is lack of access to effective, convenient, and safe treatment that enables long-term disease control and remission, as many patients experience flares as soon as they stop their current medication. This cycle of recurrence leads to disease progression ending in chronic severe AD and severe impact on HRQoL.

According to the clinician group, the place in therapy for upadacitinib would be after initial treatments for mild AD (e.g., lifestyle measures and topical steroids). In such case, upadacitinib would replace systemic therapies that are currently used off-label to treat AD, as well as phototherapy. In the clinician group's opinion, dupilumab addresses some concerns and needs of some patients, but upadacitinib may shift the paradigm due to its efficacy and ease of administration. This place in therapy judgment differs from the opinion of the clinical expert consulted by CADTH who indicated that upadacitinib should be used after a trial of systemic therapies currently used (even if off-label) for treating patients whose AD has failed to respond to TCS, such as methotrexate or cyclosporine.

The clinician group notes that upadacitinib would be best suited to treat patients with moderate to severe AD who have not responded, are not expected to respond, or have had adverse reactions to long-term use of TCS. These patients are in the most need of

intervention as they lack long-term treatment options and are at high risk of disease progression.

The outcomes measured in clinical trials, such as the vIGA-AD, are also used in clinical practice, perhaps with the exception of EASI scores, which are relatively unknown in the day-to-day practice. The clinician group mentions that a clinically meaningful response to upadacitinib would include improvements in patient-reported itch (4 point reduction on the NRS or an NRS score of less than 3), DLQI score reduction of 4 or more (or an acceptable improvement), improved patient-reported sleep quality, fewer AD-related disruptions at school and work, and a Physician Global Assessment score of 0 or 1. Importantly, a patient should not experience any severe side effects, including over sustained time periods, in order for the response to upadacitinib to be clinically meaningful.

The group suggests that a response to systemic therapy should be reassessed 12 to 16 weeks after initiation of treatment. According to input from the clinician group, the decision to discontinue treatment should be assessed based on lack of response, significant disease progression (i.e., lichenification, increased affected body surface area, and itching) and deterioration in quality of life, or if the patient experiences adverse reactions or intolerance to the medication that are deemed to be unacceptable by the patient-physician team. Treatment with upadacitinib should be interrupted if a patient develops a serious infection, or presents serious abnormal laboratory results (e.g., absolute lymphocyte count less than 500 cells/mm^3, absolute neutrophil count less than 1,000 cells/mm^3, hemoglobin less than 8 g/dL, or if drug-induced liver injury is suspected [based on hepatic transaminases]), treatment with upadacitinib may be resumed once levels return to normal. Patients with AD receiving upadacitinib would ideally be managed in any non-emergent setting that they have access to, and that has a dermatologist or allergist well-versed in managing moderate to severe AD. Referring family physicians, nurse practitioners, or other health care providers should be counselled on the appropriate referral process.

Drug Program Input

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

- relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for prescribing of therapy.

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	
Access to phototherapy seems to be limited across Canada. Is this factual or perceived among clinicians and dermatologists?	CDEC agreed with the clinical expert that phototherapy is mostly accessible in urban areas but not in rural areas and

Implementation issues	Response
	that it is important to consider this barrier in the decision-making process.
Considerations for initiation of therapy	
Would upadacitinib be initiated in patients whose AD has not responded to previous treatment with a biologic drug?	CDEC agreed with the clinical expert that from a clinical perspective, patients whose AD did not respond to dupilumab plus 1 of the immunomodulators would be candidates to receive upadacitinib, but this also would apply in those whose AD hasn't responded to dupilumab alone, although there is high uncertainty due to lack of evidence for this clinical recommendation.
Should it be required that patients had an adequate trial of (or be ineligible for) cyclosporine, methotrexate, and phototherapy before initiating upadacitinib?	CDEC noted that patients must have had an adequate trial or be ineligible for or intolerant to each of the following therapies: maximally tolerated medical topical therapies for AD combined with phototherapy (where available), and maximally tolerated medical topical therapies for AD combined with at least 1 of the 4 systemic immunomodulators (methotrexate, cyclosporine, mycophenolate mofetil, or azathioprine) before initiating upadacitinib. The clinical expert indicated that a trial of 2 of the 4 immunomodulators (methotrexate, cyclosporine, mycophenolate mofetil, or azathioprine) should be considered before initiating upadacitinib.
Will dupilumab (or other biologics approved for AD) be among the prior therapies required in the eligibility criteria for initiation of therapy with upadacitinib?	CDEC agreed with the clinical expert that dupilumab, as prior therapy before initiating upadacitinib, should not be an initiation criterion. Both drugs would have the same place of therapy in the population for this indication.
The included trials had a duration of 12 to 16 weeks, with the longest follow-up in the studies assessing up to 48 weeks. Based on the available evidence, would you consider that the long-term safety data have been established with certainty?	CDEC agreed with the clinical expert that the currently available evidence is not sufficient to establish the long-term safety profile of upadacitinib in the treatment of AD and a much longer period of follow-up is required.
The CDEC initiation criteria for dupilumab are: 1. Patients aged 12 years and older with moderate to severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. 2. Patients must have had an adequate trial or be ineligible for each of the following therapies: phototherapy (where available), methotrexate, and cyclosporine. 3. Patients who have had an adequate trial phototherapy, methotrexate, and/or cyclosporine must have documented refractory disease or intolerance. 4. The physician must provide the EASI score and Physician Global Assessment score at the time of initial request for reimbursement. 5. The maximum duration of initial authorization is 6 months.	CDEC agreed with the clinical expert that these criteria are feasible to apply to upadacitinib. The clinical expert also noted that it would be practical also to consider earlier than 6 months for the duration of the initial authorization (i.e., 16 to 20 weeks instead of 24 weeks) and proceed to assess the continuation or renewal of the indication.

Implementation issues	Response
Would consideration be given to aligning the initiation criteria of upadacitinib with that of dupilumab?	
The CDEC recommendation for dupilumab included the following 3 implementation considerations: 1. Based on the trials, moderate to severe AD is defined as an EASI score of 16 points or higher, or a vIGA-AD score of 3 or 4. 2. Adequate control and refractory disease are optimally defined using similar criteria to those used in the dupilumab RCTs, such as achieving an EASI 75. 3. Phototherapy may not be available in all jurisdictions. Geographic inability to access phototherapy should not preclude patients from accessing dupilumab if otherwise indicated. Should these 3 implementation considerations also be considered for upadacitinib?	CDEC agreed with the clinical expert that these implementation considerations are relevant for the reimbursement of upadacitinib and should be noted in the recommendation.
How would an "adequate trial" be defined in clinical practice for patients with AD who undergo therapy with phototherapy (where available), methotrexate, and cyclosporine?	The clinical expert noted to CDEC the following: • For phototherapy: the typical duration would be considered 12 weeks (3 times per week). • For methotrexate: in AD, an adequate trial of methotrexate would be 10 mg to 20 mg per week for 12 weeks • For cyclosporine: in AD an adequate trial of cyclosporine would be 2.5 mg/kg to 5 mg/kg per day for 12 weeks For methotrexate and cyclosporine, patients who achieve good response may be tapered to a lower maintenance dose before 12 weeks for both drugs, but particularly for cyclosporine. Twelve weeks is the minimum duration for both drugs to properly assess response.
How would *ineligible* be defined in clinical practice for patients with AD who are ineligible to receive therapy with methotrexate or cyclosporine?	The clinical expert noted to CDEC that risk factors or potential adverse reactions from the interventions would make patients ineligible. CDEC also noted that ineligibility is sufficiently described in the product monographs of methotrexate or cyclosporine.
Considerations for continuation or renewal of therapy	
CDEC renewal criteria for dupilumab is as follows: 1. The physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as a 75% or greater improvement from baseline in the EASI score (EASI 75) 6 months after treatment initiation. 2. The physician must provide proof of maintenance of EASI 75 response from baseline every 6 months for subsequent authorizations. Should renewal criteria of upadacitinib be aligned with that of dupilumab?	The clinical expert noted to CDEC that the renewal criteria are feasible to apply to upadacitinib, although the timing of 6 months (24 weeks) after initiation of treatment could be long for upadacitinib and consideration for shorter duration (e.g., 16 to 20 weeks) might be required, followed by every 6 months thereafter.

Implementation issues	Response
Considerations for prescribing of therapy	
Can upadacitinib be used in combination with other JAK inhibitors, biologic DMARDs, phototherapy, or immunosuppressants?	CDEC agreed with the clinical expert that upadacitinib should not be used in combination with other systemic treatments for AD (there is no evidence investigating the safety and efficacy of such combinations).
Should upadacitinib be prescribed in consultation with a dermatologist and/or specialist?	CDEC agreed with the clinical expert that a specialist would be required to diagnose, treat, and monitor patients taking upadacitinib. Appropriate specialists would include a pediatric dermatologist or a general dermatologist.

AD = atopic dermatitis; CDEC = Canadian Drug Expert Committee; DMARD = disease-modifying antirheumatic drug; EASI = Eczema Area and Severity Index; JAK = Janus kinase; RCT = randomized controlled trial; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis .

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Measure Up 1 and Measure Up 2 were 2 similar studies (n = 847 and 836, respectively) with a double-blind, placebo-controlled parallel design. Eligible patients were adults and adolescents (≥ 40 kg) with chronic AD and a documented history of inadequate response to topical AD treatments or use of systemic treatment. Both studies randomized patients to upadacitinib 15 mg, 30 mg, or placebo. The studies evaluated co-primary outcomes, the proportion of responders based on EASI 75 score and a vIGA-AD score of 0 or 1 at week 16.

The AD Up study had a similar design to the Measure Up 1 and Measure Up 2 studies, with the same inclusion criteria and population (n = 901) but using TCS in combination therapy with upadacitinib 15 mg, 30 mg, or placebo, and also using the same co-primary end points at 16 weeks.

The Heads Up study was a double-blind, double-dummy, active controlled randomized study (n = 692) comparing upadacitinib 30 mg to dupilumab 300 mg subcutaneous in adults (18 to 75 years old) with chronic AD and documented history of inadequate response to topical treatments or documented treatment with systemic therapies. This study's primary end point includes the proportion of patients achieving an EASI 75 at week 16.

Efficacy Results

The clinical expert consulted by CADTH considered outcomes of disease severity such as EASI 75, vIGA-AD, and the SCORing Atopic Dermatitis scale (SCORAD) to be critical for decision-making and clinical practice. These were also mentioned in the patient input received from patient groups. Similarly, the outcome of symptoms — measured with the pruritus NRS, POEM, and ADerm Impact Scale — HRQoL, mood, and productivity were considered among the most important elements for measurement to be applied across different domains of decision-making.

At 16 weeks of follow-up, upadacitinib showed statistically significant improvements in the co-primary end points of disease severity in the Measure Up, AD Up, and Heads Up studies.

In Measure Up 1, more patients reached an EASI 75 score in the upadacitinib 15 mg (196 [69.6%] of 281 patients) and upadacitinib 30 mg (227 [79.7%] of 285 patients) groups than in the placebo group (46 [16.3%] of 281 patients; adjusted difference versus placebo of 53.3% [95% confidence interval (CI), 46.4 to 60.2; P < 0.001] for the upadacitinib 15 mg group; 63·4% [95% CI, 57.1 to 69.8; P < 0.001] for the upadacitinib 30 mg group). When assessing EASI 90, more patients in the upadacitinib 30 mg (187 [65.8%]) and 15 mg (149 [53.1%]) groups were responders as compared to placebo (23 [8.1%]; adjusted difference of 57.8% [95% CI, 51.5 to 64.1] and 45.1% [95% CI, 38.6 to 51.7] respectively). In Measure Up 2, similarly, 166 [60.1%] of 276 patients in the upadacitinib 15 mg group and 206 [72.9%] of 282 patients in the upadacitinib 30 mg group versus 37 [13.3%] of 278 patients in the placebo group reached the EASI 75, with an adjusted difference in EASI 75 response rate versus placebo of 46.9% [95% CI, 39.9 to 53.9; P < 0.001] for the upadacitinib 15 mg group; 59.6% [95% CI, 53.1 to 66.2; P < 0.001] for the upadacitinib 30 mg group. When assessing EASI 90, more patients in the upadacitinib 30 mg (165 [58.5%]) and 15 mg (117 [42.4%]) groups were responders as compared to placebo (15 [5.4%]; adjusted difference of 53.1% [95% CI, 46.7 to 59.4] and 36.9% [95% CI, 30.6 to 43.3] respectively). Likewise, in Measure Up 1, a larger proportion of patients achieved a vIGA-AD response at week 16 in the upadacitinib 15 mg (135 [48.1%] patients) and upadacitinib 30 mg (177 [62.0%] patients) groups than the placebo group (24 [8.4%] patients) (adjusted difference versus placebo of 39.8% [95% CI, 33.2 to 46.4; P < 0.001] for the upadacitinib 15 mg group; 53.6% [95% CI, 47.2 to 60.0; P < 0.001] for the upadacitinib 30 mg group) and in Measure Up 2 (107 [38.8%] patients in the upadacitinib 15 mg group and 147 [52.0%] patients in the upadacitinib 30 mg group versus 13 [4.7%] patients in the placebo group; adjusted difference in vIGA-AD response rate versus placebo of 34.0% [95% CI, 278 to 40.2; P < 0.001] for the upadacitinib 15 mg group; 47.4% [95% CI, 41.0 to 53.7; P < 0.001] for the upadacitinib 30 mg group).

In the AD Up study, at week 16, the proportion of patients who had achieved EASI 75 was statistically significantly higher in the upadacitinib 15 mg plus TCS group (194 [64.6%] of 300 patients) and the upadacitinib 30 mg plus TCS group (229 [77.1%] of 297 patients) than the placebo group (80 [26.4%] of 304 patients; adjusted difference in EASI 75 response rate versus placebo of 38.1% [95% CI, 30.8 to 45.4; P < 0.001] for the upadacitinib 15 mg group and 50.6% [95% CI, 43.8 to 57.4; P < 0.001] for the upadacitinib 30 mg group). When assessing EASI 90, more patients in the upadacitinib 30 mg (187 [63.1%]) and 15 mg (128 [42.8%]) were responders as compared to placebo (40 [13.2%]; adjusted difference of 57.8% [95% CI, 51.5 to 64.1] and 45.1% [95% CI, 38.6 to 51.7] respectively). The proportion of patients who achieved a vIGA-AD response at week 16 was statistically significantly higher in the upadacitinib 15 mg plus TCS (119 [39.6%] patients) and upadacitinib 30 mg plus TCS (174 [58.6%] patients) groups than the placebo group (33 [10.9%] patients; adjusted difference of 28.5% [95% CI, 22.1 to 34.9] for the upadacitinib 15 mg group and 47.6% [95% CI, 41.1 to 54.0] for the upadacitinib 30 mg group; P < 0.0001 for both doses).

In the Heads Up trial, patients in the upadacitinib 30 mg showed statistically significantly higher rates of achieving EASI 75 scores (247 [71.0%]) than patients taking dupilumab 300 mg (210 [61.1%]) at week 16; the adjusted difference between groups was 10.0% (95% CI, 2.9 to 17.0; P = 0.006). This difference was no longer statistically significant at week 24, with 205 (59.5%) patients in the dupilumab group and 223 (64.2%) patients in the upadacitinib 30 mg group achieving an EASI 75 (adjusted difference of 4.6% [95% CI, -2.6 to 11.9]; P = 0.211). When assessing EASI 90 at week 16, more patients in the upadacitinib 30 mg (211 [60.6%]) group were responders as compared to the dupilumab (133 [38.8%] group; adjusted

difference of 21.8% [14.5 to 29.1]), and this difference between groups was smaller at week 24 (adjusted difference of 4.6% [95% CI, 0.5 to 15.4]; P = 0.036).

An assessment of patients with previous systemic therapies showed similar results to the base case in all studies (Measure Up1, Measure Up2, AD Up, and Heads Up trials) for the primary end points of response based on the EASI 75 at week 16, and the vIGA-AD (except for the Heads Up study where no vIGA-AD was assessed). In the subgroup of patients with prior use of a systemic treatment (e.g., steroid or biologic) for AD, the adjusted differences (95% CI) for upadacitinib 15 mg once daily and 30 mg once daily (respectively) compared with placebo for EASI 75 response at week 16 were: for Measure Up-1, 54.1% (44.1 to 64.0) and 67.6% (58.9 to 76.3); for Measure Up-2, 50.8% (41.8 to 59.9) and 61.5% (52.7 to 70.3); [redacted] and [redacted]. For Heads Up, the proportion reaching EASI 75 at week 16 was [redacted] and [redacted] for dupilumab and upadacitinib, respectively; the adjusted difference of upadacitinib 30 mg against dupilumab 300 mg was [redacted]. For vIGA-AD response the results were: for Measure Up-1, [redacted] and [redacted]; for Measure Up-2, [redacted] and [redacted]; for AD Up, [redacted] and [redacted]. Heads Up did not include a vIGA-AD assessment.

Symptoms of AD were also improved. In the Measure Up studies, the proportion of patients achieving a Pruritis NRS score of 4 or greater from baseline at week 16 was statistically significantly higher when compared to placebo for upadacitinib 15 mg (absolute risk difference from placebo [95%CI] of 40.5% [33.5 to 47.5] in Measure Up 1, and 32.6% [25.8 to 39.4] in Measure Up 2) and in the 30 mg group (48.2% [41.3 to 55.0] in Measure Up 1, and 50.4% [43.8 to 57.1] in Measure Up 2); P < 0.001 for all comparisons. The proportion of patients achieving POEM total score improvement (reduction) of at least 4 points from baseline at week 16 was also statistically significantly higher for upadacitinib 15 mg (absolute risk difference [95%CI] of 52.3% [45.2 to 59.4] in Measure Up 1, and 42.1% [34.5 to 49.8] in Measure Up 2) and 30 mg (58.6% [51.9 to 65.3] in Measure Up 1 and 54.7% [47.7 to 61.7] in Measure Up 2) against placebo (P < 0.001 for all comparisons). Improvements were also observed in ADerm Impact Scale skin pain, sleep, emotional, and daily activities domains (P < 0.001 for all comparisons). No subgroup analyses were performed on symptoms outcomes.

In AD Up, the results were similar to Measure Up, where the proportion of patients achieving a Pruritis NRS score of 4 or greater from baseline at week 16 was statistically significantly higher when compared to placebo for upadacitinib 15 mg (absolute risk difference from placebo of 36.8% [95% CI, 29.7 to 43.8]) and 30 mg (48.8% [95% CI, 41.9 to 55.7]); P < 0.001 for all comparisons. The POEM total score improvement of at least 4 points from baseline was also statistically significantly higher for upadacitinib 15 mg (absolute risk difference of 40.2% [95% CI, 33.0, 47.4]) and 30 mg (44.9% [95% CI, 37.9 to 51.8]) against placebo; P < 0.001 for all comparisons. Improvements were also observed in ADerm Impact Scale skin pain, sleep, emotional, and daily activities domains (P < 0.001 for all comparisons).

When compared to dupilumab (Heads Up study), the proportion of patients achieving a Pruritis NRS score of 4 or greater at week 16 was statistically significantly higher in the upadacitinib 30 mg group (55.2%) as compared to dupilumab 300 mg (35.9%) with an absolute risk difference of 19.3% (95% CI, 11.9 to 26.7; P < 0.001). The risk difference decreased at week 24 to 8.3% (95% CI, 0.8 to 15.8), although it was still statistically significant (P = 0.030).

HRQoL, assessed by the DLQI score, was also improved more frequently in the upadacitinib 15 and 30 mg groups than in the placebo group in the Measure Up and the AD Up studies, but

not when assessed with the generic EQ-5D 5-Levels index. Mood and work productivity were similarly improved in the upadacitinib groups versus placebo. Absenteeism domains were not significantly statistically different between groups. No subgroup analyses were performed on these outcomes.

Harms Results

Upadacitinib 15 mg and 30 mg doses in all studies were well tolerated as compared to placebo at week 16, and without significant increases in adverse events (AEs) or serious adverse events (SAEs) up to the latest follow-up of 52 weeks in the blinded extension studies. The incidence of SAEs and AEs leading to study drug discontinuation were similar among groups except for in the Heads Up study. The most frequently reported AEs were acne, upper respiratory tract infection, nasopharyngitis, headache, elevation in creatine phosphokinase levels, and AD. No deaths were reported. No subgroup analyses based on prior exposure to systemic treatment (e.g., steroid or biologic) for AD were performed for AEs.

In the AD Up study, the most frequently reported AEs (≥ 5% in any treatment group) were acne, nasopharyngitis, upper respiratory tract infection, oral herpes, elevation of blood creatine phosphokinase levels, headache, and AD. Acne was more frequent in the upadacitinib groups (10% to 14% in the 15 mg and 30 mg groups, respectively) than placebo (2%) at week 16. No deaths were reported.

In the Heads Up study, the safety profile of upadacitinib was similar to the Measure Up and AD Up studies. The rates of SAEs and AEs leading to study drug discontinuation were 2.9% and 1.2% for upadacitinib and 1.2% and 1.2% for dupilumab, respectively. One death was reported in a patient treated with upadacitinib due to influenza-associated bronchopneumonia. The most frequently reported AE with upadacitinib was acne (15.8%), whereas this AE was only reported by 2.6% of patients receiving dupilumab. The most frequently reported AE with dupilumab was conjunctivitis (8.4%), whereas this AE was only reported by 1.4% of those receiving upadacitinib. Other AEs more common in the upadacitinib group were serious infection (1.1% versus 0.6%), eczema herpeticum (0.3% versus 0%), hepatic disorders (2.9% vs 1.2%), and herpes zoster (2.0% versus 0.9%). Also, rates of anemia (2.0% versus 0.3%), neutropenia (1.7% versus 0.6%), and creatinine phosphokinase elevations (6.6% versus 2.9%) were higher for upadacitinib than dupilumab.

Critical Appraisal

Randomization and allocation concealment were properly completed, resulting in a similar distribution of baseline demographics and disease characteristics variables between the treatment groups in each trial, without important imbalances. Blinding of patients and study personnel was appropriately maintained. However, given that a placebo was used in several studies, it is possible patients may have been potentially unblinded or may have been aware of their assignments due to improvement or lack of improvement (placebo) in AD over the study period. There is the possibility that, in the Heads Up trial, certain adverse effects (injection site, hypersensitivity reactions, conjunctivitis) that would be known to be at higher risk with dupilumab may have also potentially resulted in unblinding, which could have biased the results of patient-reported outcomes such as HRQoL. However, the co-primary end points are relatively objective, and risk of bias would be small.

The co-primary outcomes were based on the vIGA-AD and EASI scores, both reliable and valid for the assessment of severity and extent of AD. The co-primary end points were appropriately analyzed using the intention-to-treat population. Secondary end points were

analyzed based on complete case analyses. This is expected to introduce some risk of bias in favour of upadacitinib (as more complete data were available for upadacitinib due to lower discontinuations and drop-outs) because the groups may no longer be balanced in characteristics, and data observed from the incomplete cases are discarded (i.e., patients who are responding to treatment and have limited AEs may be more likely to stay in the study and contribute data to the end points). Controlling for multiplicity was appropriate for the primary and secondary end points of all trials by using a graphical multiple testing procedure. The greatest number of patients that discontinued the intervention were within the placebo groups in the Measure Up and AD Up trials. This introduces the potential for bias against the null (i.e., toward an inflated efficacy of upadacitinib) due to the analytical approaches used as more patients in the placebo group would have been imputed as nonresponders. However, sensitivity analyses were based on multiple imputation, the tipping point approach, and on the per-protocol population, with similar conclusions as the primary analyses. Several subgroup analyses were properly specified a priori and conducted across the trials (e.g., based on baseline vIGA-AD, baseline EASI, previous systemic therapy, age, sex, among others) showing similar results.

The population in the included pivotal studies seem to be generalizable to adults and adolescents in the Canadian population who have AD. However, when considering the applicability of the results for the population of patients previously treated with systemic therapies (i.e., the approved indication for upadacitinib), only a proportion of the patients included in the pivotal studies was similar to the approved Health Canada indication. Furthermore, the information from the pivotal studies for the 30 mg dose also represents a proportion of the population, and data to inform the approved indication are lacking, this is, data estimating the effects of upadacitinib in patients with AD who are switched from 15 mg to 30 mg if an adequate response (e.g., EASI 75) is not achieved. In addition, there were no clinical studies that studied a dose de-escalation to 15 mg once daily in patients who achieved a response to upadacitinib 30 mg once daily. This lack of evidence adds uncertainty to the generalizability of results in the population for which the indication would be applicable.

In all pivotal trials included in this CADTH review, an assessment of the subgroup of patients with previous systemic therapies showed similar results to the base case for the primary end points of response based on the EASI 75 at week 16, and the vIGA-AD (except for the Heads Up study where no vIGA-AD was assessed). Although this implies that the beneficial effect of upadacitinib in the previously treated population is reflective of the overall base case population, this should be interpreted with caution because it was not an a priori specification for this subgroup analysis and can be underpowered for drawing conclusions. The clinical expert consulted by CADTH suggested that the response to upadacitinib would likely be similar for those with and without prior exposure to a systemic therapy for AD.

The population in Measure Up 1 appeared to have slightly less severe AD than in the rest of the studies. The rest of the baseline and demographic characteristics were overall similar between studies. The adolescent population analyzed in these included studies (except for the Heads Up trial) overall mirrored the results from the adult population; however, the adolescent population was relatively small in the included trials. More evidence will be needed in underrepresented population such as those who are Black, Indigenous, and Asian. Also, the duration of trials might not be long enough to assess long-term outcomes (harms), and as patients in the Measure Up and AD Up studies were "dupilumab naïve," more evidence is needed to assess the response of upadacitinib in patients who are previously treated with dupilumab.

Indirect Comparisons

Description of Studies

Three ITCs, 2 sponsor-submitted (ITC1, ITC2) and 1 obtained from the CADTH literature search (ITC3, conducted by the Institute for Clinical and Economic Review), were included to provide an increased perspective on the body of evidence by including indirect comparisons of upadacitinib against dupilumab and other systemic therapies. All performed an analysis of upadacitinib and its efficacy against other common comparators using Bayesian network meta-analyses (NMAs).

The first is an NMA aiming at comparing upadacitinib 15 mg or 30 mg (with or without TCS) against dupilumab in adults or adolescents with moderate to severe AD whose disease has had an inadequate response to cyclosporine A or other systemic therapy (namely: ITC 1 – post cyclosporine). The second is an NMA on a comprehensive published RCT evidence base to determine the comparative effectiveness of upadacitinib 15 mg and 30 mg versus other immunomodulators in patients with moderate to severe AD as monotherapy (not concomitantly receiving TCS) and as combotherapy (concomitantly receiving TCS). The third is an NMA report from the Institute for Clinical and Economic Review evaluating systemic therapies (abrocitinib, baricitinib, upadacitinib, tralokinumab, dupilumab) with or without topical therapies in adults and children (≥ 12 years old) with moderate to severe AD.

Results

Overall, the results from the 3 ITCs suggest that upadacitinib 30 mg and 15 mg are among the most effective systemic therapies for reducing the severity and symptoms of moderate to severe AD in adults and adolescents, either as monotherapy or in combination with TCS.

As monotherapy, based on results from ITC1, upadacitinib 30 mg and upadacitinib 15 mg demonstrated [redacted]. From the ITC2, upadacitinib 30 mg was superior to all comparators (abrocitinib 100 mg, dupilumab 300 mg, baricitinib 2 mg, baricitinib 4 mg, tralokinumab 300 mg) on all outcomes except against abrocitinib 200 mg where no difference was detected in the EASI 75 scores and pruritus NRS. Upadacitinib 15 mg was superior to abrocitinib 100 mg, dupilumab 300 mg, baricitinib 2 mg, baricitinib 4 mg, and tralokinumab 300 mg, with no difference detected against abrocitinib 200 mg, and only inferior to upadacitinib 30 mg in both the EASI 75 and vIGA-AD scores. The ITC3 Institute for Clinical and Economic Review report showed that upadacitinib 30 mg was superior to upadacitinib 15 mg, abrocitinib 100 mg, dupilumab 300 mg, baricitinib 1 mg, baricitinib 2 mg, and tralokinumab 300 mg; with no difference detected against abrocitinib 200 mg when assessing the EASI 75 and vIGA-AD scores. Upadacitinib 15 mg was superior to abrocitinib 100 mg, baricitinib 1 mg, baricitinib 2 mg, and tralokinumab 300 mg; with no difference detected against abrocitinib 200 mg and dupilumab 300 mg, and only inferior to upadacitinib 30 mg in the EASI 75 and vIGA-AD scores.

When combination therapy with TCS was assessed, the ITC1 showed [redacted]. The ITC2 demonstrated that [redacted]. The ITC 3 demonstrated superiority of upadacitinib 30 mg against upadacitinib 15 mg, abrocitinib 200 mg, abrocitinib 100 mg, dupilumab 300 mg, baricitinib 2 mg, and tralokinumab 300 mg in all EASI 75, vIGA-AD, and pruritus NRS scores. Only when evaluating the vIGA-AD score, no difference was detected between abrocitinib 200

mg and upadacitinib 30 mg. Upadacitinib 15 mg was only inferior to upadacitinib 30 mg, and superior to abrocitinib 100 mg, baricitinib 2 mg, and tralokinumab 300 mg, and no difference was detected when compared to dupilumab and abrocitinib 200 mg for all outcomes.

Effect estimates from ITC3 had, in general, lower odds ratio values when compared to ITC1 and ITC2, but overall, results were similar between the 3 ITCs, with superiority of upadacitinib 30 mg over upadacitinib 15 mg, dupilumab and the other comparators, and no difference detected against abrocitinib 200 mg.

No harm data were analyzed in any of the ITCs.

Critical Appraisal

The limitations from the 3 ITCs stem from uncertainty in the effect estimates due to imprecision (wide and overlapping credible intervals among comparisons) and baseline heterogeneity. It is uncertain how upadacitinib relates to other relevant comparators in the population previously treated with systemic therapies (i.e., the approved indication for upadacitinib). Only 1 ITC (ITC1) evaluated patients previously exposed to systemic therapies (cyclosporine). Although the comparison in this ITC is exclusively of upadacitinib versus dupilumab and it limits the scope (generalizability) to other comparisons, the dupilumab comparison is still relevant as it is a commonly prescribed and reimbursed AD treatment in Canada. Conclusions regarding the long-term efficacy of upadacitinib compared to the active comparators relevant to this review cannot be drawn as the NMA used study results collected over a relatively short duration compared to the chronic nature of AD. There is also uncertainty due to the inherent heterogeneity across trials in the networks. The robustness of the comparative efficacy was further compromised by the lack of precision in the findings; consequently, results from the ITCs must be interpreted with caution. Moreover, no information was obtained regarding the comparative safety when comparing to other active comparators. In addition, no conclusion could be drawn on the HRQoL outcomes.

Other Relevant Evidence

Description of Studies

Three extension studies of the included studies were reported in the submission. Measure Up 1 to 52, Measure Up 2 to 52, and AD Up 52 are a phase III, randomized, double-blind, placebo-controlled multicenter studies in adolescents (12 to 17 years) and adults (18 to 75 years) with moderate to severe AD. The Measure Up studies included a 35-day screening period, a 16-week double-blind period, a blinded extension period of up to week 136, and a 30-day follow-up visit. AD Up (week 52 data cut-off was December 18, 2020) included a 35-day screening period, a 16-week double-blind period, a blinded extension period of up to week 136, and a 30-day follow-up visit. At week 16, patients in the placebo group were re-randomized in a 1:1 ratio to receive daily oral doses of upadacitinib 30 mg or upadacitinib 15 mg in a blinded fashion up to week 136 in the blinded extension period.

Efficacy Results

Patients in Measure Up 1 to 52, Measure Up 2 to 52, and AD Up 52 maintained response in the co-primary end points. For instance, in Measure Up 1 to 52, 59.2% and 62.5% of the patients who started upadacitinib 15 mg and 30 mg once daily, respectively, maintained a vIGA-AD response of 0 or 1 at week 52; and 82% and 84.9% of the patients who started upadacitinib 15 mg and 30 mg once daily, respectively, maintained an EASI 75 response at week 52. In Measure Up 2 to 52, 52.6% and 65.1% of the patients who started upadacitinib 15 mg and 30

mg once daily, respectively, maintained a vIGA-AD response of 0 or 1 at week 52; and 79.1% and 84.3% of the patients who started upadacitinib 15 mg and 30 mg once daily, respectively, maintained an EASI 75 response at week 52. In AD Up 52, 46.3% and 55.7% of the patients who started upadacitinib plus TCS 15 mg and 30 mg once daily, respectively, maintained a vIGA-AD response of 0 or 1 at week 52; and 70.8% and 83.5% of the patients who started upadacitinib plus TCS 15 mg and 30 mg once daily, respectively, maintained an EASI 75 response at week 52.

Harms Results

In Measure Up 1 to 52, a total of 648 patients had at least 1 AE during the study, most commonly related to acne (16.7%), upper respiratory tract infections (14.4%), and nasopharyngitis (13%). In Measure Up 2 to 52, a total of 606 patients (75.8%) had at least 1 AE during the study. The most common AE was acne (16.8%). In AD Up, a total of 731 patients had at least 1 treatment-emergent AE during the study, most commonly related to nasopharyngitis (20.9%) and acne (16.1%). No deaths were reported. SAEs included creatine phosphokinase elevations. The most common notable harms were hepatic disorder (6.1%), herpes zoster (5.3%), creatine phosphokinase elevation (8.2%), and serious infection (3.5%).

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree and Markov model hybrid
Target population	Adolescents and adults (patients aged 12 years or over) with AD who are eligible for conventional systemic therapies
Treatments	Upadacitinib: 15 mg and 30 mg
Submitted price	Upadacitinib, 15 mg: $48.68 per tablet Upadacitinib, 30 mg: $74.00 per tablet
Annual treatment cost	Upadacitinib, 15 mg: $17,768 Upadacitinib, 30 mg: $27,010
Comparators	Best supportive care (comprised of a basket of emollients, low-to-mid potency TCS, rescue therapy). Dupilumab
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	10 years
Key data source	The impact of treatment on clinical response at 16 weeks was informed by network meta-analyses for upadacitinib as monotherapy (MEASURE UP-1, MEASURE UP-2) or in combination with TCS (AD Up)

Component	Description
Key limitations	• The sponsor's base case does not reflect the intended clinical usage of upadacitinib. The recommended starting dose of upadacitinib is 15 mg daily, with an increase to 30 mg for patients with an inadequate response; patients with severe AD may start treatment on upadacitinib 30 mg. The sponsor's base case considers the cost-effectiveness of each dose separately and does not allow patients to transition between doses. The sponsor submitted a scenario analysis to reflect this dosing strategy; however, interpretation of the findings is limited by a lack of clinical data and structural limitations within the model. • The target population of the sponsor's base case (patients eligible for systemic therapy) is not aligned with the indicated population (after a trial of systemic therapy). Upadacitinib is expected to be used in combination with TCS, not as monotherapy as assumed by the sponsor. • The use of clinical efficacy data assessed after 16 weeks of treatment may overestimate the incremental effectiveness of upadacitinib compared with dupilumab, owing to a longer onset of effect for dupilumab; this biases the ICER in favour of upadacitinib. • The cost-effectiveness of upadacitinib among adolescents is unknown. The sponsor's model assumed a cohort starting age of 33.9 years, based on pooled data from the Measure Up and AD Up trials. Data from the MEASURE UP-1 trial suggest that there may be a difference in the effect of upadacitinib on HRQoL between adults and adolescents, and treatment adherence may vary between adults and adolescents. The model lacked the flexibility needed to assess cost-effectiveness by age group. • Relevant comparators for the target population, such as immunosuppressants (e.g., methotrexate and cyclosporine), retinoids, and phototherapy were not included as comparators in the model. • The long-term effectiveness of upadacitinib is highly uncertain. The sponsor assumed that the long-term effectiveness of upadacitinib (52-week treatment response, treatment discontinuation, effectiveness waning) would be equivalent to dupilumab. This assumption was not justified, and long-term data for upadacitinib are not available. • The durability of treatment response (HRQoL waning among treatment responders) was adopted from multiple sources without accounting for differences in patient characteristics or study designs. • The sponsor adopted a 10-year analysis horizon, which is insufficient to capture all costs and effects associated with treatment for AD. • Adherence to upadacitinib was based on clinical trial data, which likely overestimates adherence in clinical practice. The effects of adherence on health outcomes were not considered. • The health state utility values lacked face validity in that the baseline value was lower than reported in previous analyses, the utilities were unnecessarily mapped from the EQ-5D-5L to EQ-5D-3L, and multiple utility values were submitted for some health states. • The sponsor assumed that the impact of adverse events would be captured by health state utility values, which is unlikely. The model did not include all adverse events deemed important by patients or clinical experts consulted for this review. • The sponsor's model employed poor modelling practices, preventing CADTH from fully validating the model and its findings.
CADTH reanalysis results	• The cost-effectiveness of the Health Canada–recommended dosing strategy could not be estimated owing to a lack of clinical data and limitations with the sponsor's model. As such, the cost-effectiveness of upadacitinib is unknown. CADTH undertook exploratory reanalyses to correct the sponsor's model using best available evidence; however, the validity and interpretability of the results are limited. CADTH notes that all reanalysis results reflect the adult population only. • CADTH reanalyses included assuming that upadacitinib will be used among patients with prior exposure to systemic therapies, assuming that upadacitinib and dupilumab will be used in combination with TCS, adopting a lifetime horizon, assuming treatment waning, and, adopting

Component	Description
	alternative assumptions about the durability of treatment response with BSC. • CADTH was unable to address the lack of comparative clinical data for omitted relevant treatment comparators, the cost-effectiveness of upadacitinib among adolescents or by disease severity, the impact of adverse events on the ICER, or the lack of long-term comparative effectiveness data. • In CADTH's exploratory reanalyses, upadacitinib 15 mg + TCS was associated with an ICER of $48,616 compared with BSC, and upadacitinib 30 mg + TCS was associated with an ICER of $372,226 compared with upadacitinib 15 mg. Dupilumab was dominated by upadacitinib 15 mg + TCS. • The results of the CADTH exploratory reanalyses are highly uncertain, due to several key and potentially influential limitations that could not be addressed through reanalysis. Key among these is the lack of clinical data pertaining to the recommended dosing strategy, the potential bias in favour of upadacitinib 30 mg versus dupilumab due to the timing of assessments in the MEASURE UP trial, assumptions about the durability of treatment, and assumptions about adherence to treatment beyond the duration of the trial evidence.

AD = atopic dermatitis; BSC = best supportive care; EQ-5D-3L = EQ-5D 3-Level; EQ-5D-5L = EQ-5D 5-Level; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; TCS = topical corticosteroids.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: The estimated budget impact is not reflective of expected clinical use of upadacitinib; there is high uncertainty around assumptions on market share distributions of upadacitinib; the proportion of patients who receive upadacitinib 30 mg versus upadacitinib 15 mg is not reflective of clinical use; the number of individuals eligible for public drug plan coverage is underestimated; and adherence to treatment with subcutaneous injection is likely underestimated.

CADTH reanalysis included assuming a greater proportion of patients taking upadacitinib 30 mg, using the proportion of patients eligible for coverage to calculate market size, and assuming higher adherence for dupilumab. Based on CADTH reanalyses, the budget impact to the public drug plans of introducing upadacitinib for patients with moderate to severe AD is expected to yield cost savings of $12,321,887 in year 1; $19,926,427 in year 2; and $30,000,815 in year 3, for a 3-year total cost savings of $62,249,129. The estimated budget impact is sensitive to treatment adherence, the proportion of patients taking upadacitinib 15 mg versus upadacitinib 30 mg, and market share distribution.

CDEC Information

Members of the Committee

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

Initial meeting date: February 24, 2022

Regrets: None

Conflicts of interest: None

Reconsideration meeting date: May 26, 2022

Regrets: One expert committee member did not attend.

Conflicts of interest: None