Canadian Journal of Health Technologies

CADTH

September 2022 Volume 2 Issue 9

CADTH Reimbursement Recommendation

Abrocitinib (Cibinqo)

Indication: For the treatment of patients aged 12 years and older with refractory moderate to severe atopic dermatitis, including the relief of pruritus, who have had an inadequate response to other systemic drugs (e.g., steroid or biologic), or for whom these treatments are not advisable. Abrocitinib can be used with or without medicated topical therapies for atopic dermatitis

Sponsor: Pfizer Canada ULC

Final recommendation: Reimburse with conditions

CADTH

ISSN: 2563-6596

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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 Cibinqo?

CADTH recommends that Cibinqo should be reimbursed by public drug plans for the treatment of patients aged 12 years and older with refractory moderate to severe atopic dermatitis (AD), including for the relief of pruritus, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Cibinqo 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?

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

Why Did CADTH Make This Recommendation?

- In 4 clinical trials, treatment with Cibinqo reduced AD severity and symptoms compared to treatment with placebo.
- Cibinqo may meet some of the needs that are important to patients, including reducing AD severity and symptoms and improving health-related quality of life (HRQoL).
- Cibinqo is not considered cost-effective compared to standard of care. Economic evidence suggests that a reduction in price of 52% to 56% would be needed to reach this threshold.
- Based on public list prices, Cibinqo will save public drug plans $50,040,374 over 3 years. Depending on the negotiated price of Dupixent, a higher price reduction may be needed and Cibinqo may no longer be cost-saving.

Additional Information

What Is AD?

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 AD

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 Cibinqo Cost?

Treatment with Cibinqo (abrocitinib) is expected to cost approximately $17,765 to $19,882 annually per patient.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that abrocitinib be reimbursed for the treatment of patients aged 12 years and older with refractory moderate to severe AD, including the relief of pruritus, who have had an inadequate response to other systemic drugs (e.g., steroid or biologic), or for whom these treatments are not advisable, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Four double-blind randomized clinical trials (RCTs) demonstrated that, compared with placebo, 12 or 16 weeks of treatment with abrocitinib was associated with statistically significant and clinically meaningful improvements in a range of outcomes that are important in the management of AD, including overall severity of AD (Eczema Area and Severity Index [EASI] and Investigator's Global Assessment [IGA]) response), severity of itching (severity of peak pruritus numerical rating scale [PP-NRS] response), symptoms (Patient-Oriented Eczema Measure [POEM] and Pruritus and Symptoms Assessment for Atopic Dermatitis [PSAAD]), HRQoL (Dermatology Life Quality Index [DLQI] and Children's Dermatology Life Quality Index [CDLQI]), fatigue (Functional Assessment of Chronic Illness Therapy Fatigue Scale [FACIT-F]), and patient-reported anxiety and depression. These trials included the use of abrocitinib as monotherapy (JADE MONO-1 [N = 387] and JADE MONO-2 [N = 391]) and as combination therapy (JADE COMPARE [N = 838 adults] and JADE TEEN [N = 287 adolescents]). In a pre-specified subgroup analysis based on prior exposure to at least 1 systemic immunosuppressant for AD for the co-primary end points of each trial (i.e., EASI-75 and IGA response), the 200 mg dose of abrocitinib consistently demonstrated benefit compared with placebo, with results that were similar to the primary analyses; however, there was greater uncertainty with the 100 mg once daily dosage. One active-controlled trial (JADE DARE [N = 727]) demonstrated that abrocitinib 200 mg once daily was superior to dupilumab for improving symptoms in the initial weeks after starting treatment, but that there were no significant differences between the 2 drugs at 26 weeks.

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 abrocitinib appears to address some of these outcomes.

Using the sponsor-submitted price for abrocitinib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for abrocitinib 100 plus standard of care (SoC) was $156,735 per quality-adjusted life-year (QALY) compared with SoC, while the ICER for abrocitinib 200 plus SoC was $231,013 per QALY compared to abrocitinib 100 plus SoC, for the treatment of refractory moderate to severe AD in patients who have had an inadequate response to other systemic drugs. At this ICER, abrocitinib is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for the treatment of moderate to severe AD among patients who have had an inadequate response to other systemic drugs. A reduction in price of at least 52% to 56% is required for abrocitinib to be considered cost-effective at a $50,000 per QALY threshold.

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 agents. Concerns about their long-term safety continue; however, clinical experience with systemic immunomodulators is extensive and the costs are modest compared to novel agents. CDEC accepted the opinion of the clinical expert and assessments of practice in other jurisdictions, and considered that at least one conventional immunomodulatory agent be attempted before abrocitinib is used for refractory AD, particularly as information about the long-term safety of the latter is awaited. In addition, in the trials reviewed by CDEC, the percentage of patients with prior exposure to at least one systemic therapy for AD was 48.3% in JADE MONO-1, 41.4% in JADE MONO-2, 43.2% in JADE COMPARE, 47.9% in JADE DARE, 25.6% in JADE TEEN, and 59.5% in JADE REGIMEN.	1. Phototherapy may not be available in all jurisdictions. Geographic inability to access phototherapy should not preclude patients from accessing abrocitinib if otherwise indicated. 2. Adequate control and refractory disease are optimally defined using similar criteria to those used in the abrocitinib trials, such as achieving an 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/day to 5 mg/kg/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 mg/kg/day to 2.5 mg/kg/day for 12 weeks
2. The physician must provide the EASI score and Investigator (Physician) Global Assessment score at the time of initial request for reimbursement.	JADE MONO-1, JADE MONO-2, JADE COMPARE, JADE TEEN, and JADE REGIMEN studies enrolled patients with an EASI score of 16 points or higher, and an Investigator (Physician) Global Assessment score of 3 or higher.	—

Reimbursement Condition	Reason	Implementation Guidance
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.	The clinical expert noted to CDEC that in clinical practice, the response to treatment is assessed 16 to 20 weeks after initiating abrocitinib, then every 6 months thereafter. The primary end point evaluation in the pivotal studies was EASI-75.	—
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 abrocitinib 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. Abrocitinib should not be used in combination with phototherapy, any immunomodulatory agents (including biologics) or other JAK inhibitor treatment for moderate to severe AD.	There is no evidence to demonstrate a beneficial effect of abrocitinib when used in combination with phototherapy, any immunomodulatory agents (including biologics), or other JAK inhibitor treatment for moderate to severe AD.	—
Pricing		
7. A reduction in price	The ICER for abrocitinib 100 + SoC is $156,735 per QALY when compared with SoC alone. The ICER for abrocitinib 200 + SoC is $231,013 per QALY when compared with abrocitinib 100 + SoC. A price reduction of 52% to 56% would be required for abrocitinib to be able to achieve an ICER of $50,000 per QALY.	—

Reimbursement Condition	Reason	Implementation Guidance
Feasibility of Adoption		
8. The feasibility of adoption of abrocitinib must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimates.	—

AD = atopic dermatitis; EASI = Eczema Area and Severity Index; ICER = incremental cost-effectiveness ratio; JAK = Janus kinase; QALY = quality-adjusted life-year; SoC = standard of care.

Discussion Points

- All trials enrolled patients with moderate to severe AD and an inadequate response to topical AD therapies. This is reflective of the indication that was initially submitted to Health Canada and CADTH; however, the approved indication reflects a more restrictive population (i.e., those with refractory moderate to severe AD and an inadequate response to other systemic drugs). The sponsor conducted pre-specified subgroup analyses based on prior exposure to at least 1 systemic immunosuppressant for AD for the co-primary end points of each trial (i.e., EASI-75 and IGA response). The clinical expert noted that results from the subgroup analyses suggested that the response to abrocitinib would likely be similar regardless of 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, or an Investigator (Physician) Global Assessment score of 3 or higher.
- The clinical expert noted to CDEC that in clinical practice, medicated topical therapies would continue to be used in combination with abrocitinib.
- One indirect treatment comparison (ITC) compared abrocitinib with dupilumab in adults or adolescents with moderate to severe AD with prior exposure to at least 1 systemic therapy for AD. This ITC suggested that, when used as monotherapy, abrocitinib 200 mg once daily was superior to dupilumab 300 mg once every 2 weeks for EASI-75 response, although there was considerable uncertainty in the estimates of effect for IGA response. However, a conclusion regarding the long-term efficacy of abrocitinib 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 long-term efficacy and safety of abrocitinib.
- All drug costs in the economic analysis are based on publicly available list prices. The cost-utility analysis and budget impact analysis are both highly sensitive to the price of dupilumab. Depending on the negotiated price of dupilumab, a higher price reduction may be required for abrocitinib to be considered cost-effective at a WTP threshold of $50,000 per QALY, and the estimate of budget impact may no longer imply cost savings.

Background

Atopic dermatitis (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 treatment are to manage and prevent flares. The treatments include general skin care and topical anti-inflammatory medication (topical corticosteroids [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 in moderate to severe AD that is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Abrocitinib is a selective Janus kinase 1 (JAK1) inhibitor indicated for the treatment of patients 12 years and older with refractory moderate to severe AD, including the relief of pruritus, who have had an inadequate response to other systemic drugs (e.g., steroid or biologic) or for whom these treatments are not advisable. The product monograph states that abrocitinib can be used with or without medicated topical therapies for AD. The product monograph for abrocitinib contains black box warnings regarding the risk of serious infections, malignancies, and thrombosis. It is recommended that treatment with abrocitinib should be interrupted if a patient develops a serious infection, sepsis, or opportunistic infection, until the infection is controlled. Abrocitinib is available as 50 mg, 100 mg, and 200 mg oral tablets. The dosage recommended in the product monograph is 100 mg or 200 mg orally once daily, for adolescents and adults under 65 years of age, based on individual goals of therapy and the potential risk for adverse reactions. For patients using the 200 mg once daily dosage, after symptom control is achieved at week 12, consider dose reduction to 100 mg once daily. Relative to patients who maintained the 200 mg dose, the risk of occurrence of serious adverse reactions decreased in patients who reduced their dose to 100 mg beyond 12 weeks. If symptom control is lost after dose reduction, the dose can be increased to 200 mg. Exceeding a daily dosage of 200 mg is not recommended. The recommended starting dose for patients who are at least 65 years of age is 100 mg. In patients with moderate (eGFR 30 to < 60 mL/min) or severe (eGFR < 30 mL/min) renal impairment, the recommended dose of abrocitinib is to be reduced by 50%.

Sources of Information Used by the Committee

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

- a review of 6 double-blind RCTs (5 placebo-controlled and 1 active-controlled), 1 long-term extension phase study, and 3 ITCs

- patients' perspectives gathered by patient groups, the Canadian Skin Patient Alliance (CSPA), Eczéma Québec, and the Eczema Society of Canada (ESC)
- input from public drug plans that participate in the CADTH review process
- a clinical specialist with expertise diagnosing and treating patients with AD
- 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 CSPA, Eczéma Québec, and the ESC. Eczéma Québec and CSPA developed and circulated a web-based survey through both organizations' newsletters and other channels (56 respondents). ESC gathered survey data from more than 3,000 Canadians who live with AD on topics including quality of life impact, experience with systemic treatments, the AD patient journey, and experience with itch related to AD.

The vast majority of patients surveyed reported symptom experience that included itching, redness of the skin, repeated rashes, frequent scratching, dry or rough skin, cracked skin, flaking, bleeding, and thickening of the skin. Itch was considered the most burdensome symptom of AD, often impacting the ability of patients to sleep. The patient groups also reported that AD had a significant negative impact on many aspects of patients' day-to-day lives, including ability to work or attend school, and participation in social interactions. The physical and quality of life impact of AD can, in turn, cause patients to experience psychological distress. Patients are seeking treatments that will reduce itch, decrease the occurrence of flares, reduce inflammation and rashes, and improve their ability to sleep and their overall quality of life. Patients, especially those who are adolescents, want to be able to have the confidence to be more outgoing and social, and patients with skin of colour want to avoid the visible skin pigment changes that can result from scratching, flares, and scarring associated with AD.

Patients affected by AD must often try multiple treatment options to find the right one for their circumstances, and these circumstances can change over time. The patient groups emphasized the importance of having multiple treatment options available to ensure that the specific circumstances of each patient can be addressed.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical expert consulted by CADTH noted that abrocitinib is potentially a useful addition to the currently available therapeutic options for AD. Abrocitinib may be particularly useful for patients who have contraindications to, experience adverse effects from, or who are unresponsive to the use of off-label immunosuppressive agents. Abrocitinib could also provide another treatment option for patients who have been treated with dupilumab but have demonstrated a suboptimal response, developed severe conjunctivitis or other ocular side effects from dupilumab, and are intolerant to injections (e.g., due to severe injection site reactions), and/or those patients who would prefer an orally administered treatment.

The clinical expert noted abrocitinib should be used as an add-on therapy and that all patients should continue regimens involving emollients, TCs, and/or topical calcineurin inhibitors (TCIs). Abrocitinib should not be used in combination with off-label immunosuppressives or dupilumab. The clinical expert believed that many specialists would consider a trial of methotrexate and cyclosporine before initiating treatment with abrocitinib.

The clinical expert suggested that patients less suitable for treatment with abrocitinib would be those with AD who are well controlled with topical therapy, phototherapy, and/or intermittent off-label immunosuppressive therapy, as well as those who are currently well controlled with dupilumab. Abrocitinib should be avoided in patients with potential contraindications to JAK 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.

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, EASI-75 after 16 weeks of treatment is a reasonable measure of response. In the opinion of the clinical expert, patients who initiate treatment with abrocitinib would be re-evaluated after 16 weeks (depending on the ability to arrange appointments). 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 could be re-evaluated after 20 weeks following initiation of the drug.

The factors anticipated by the clinical expert to be used as criteria for discontinuation included failure to achieve a 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 abrocitinib, treatment-emergent adverse effects (e.g., lymphopenia, neutropenia, arterial thrombosis, or venous thromboembolism [VTE]), 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 abrocitinib. Appropriate specialists will include pediatric dermatologists, general dermatologists, or pediatricians with experience and interest in AD.

Clinician Group Input

No clinician groups responded to the call for input for the review of abrocitinib.

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 impact the implementation of a CADTH recommendation for abrocitinib:

- relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions.

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 that it is important to consider this barrier in the decision-making process.
Considerations for Initiation of Therapy	
Would abrocitinib 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 one of the immunomodulators would be candidates to receive abrocitinib, 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 abrocitinib?	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 one of the 4 systemic immunomodulators (methotrexate, cyclosporine, mycophenolate mofetil, or azathioprine) before initiating abrocitinib. The clinical expert indicated that a trial of 2 of the 4 immunomodulators (methotrexate, cyclosporine, mycophenolate mofetil, or azathioprine) should be considered before initiating abrocitinib.
The CDEC initiation criteria for dupilumab are: 1. Patients must be those aged 12 years and older with moderate to severe AD, whose disease is not adequately controlled with topical prescription therapies, or for whom 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. Should consideration be given to aligning the initiation criteria of abrocitinib with that of dupilumab?	CDEC agreed with the clinical expert that these criteria are feasible to apply to abrocitinib. The clinical expert noted that it would also be practical 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
Will dupilumab (or other biologics approved for AD) be among the prior therapies required in the eligibility criteria for initiation of therapy with abrocitinib?	CDEC agreed with the clinical expert that dupilumab, as prior therapy before initiating abrocitinib, should not be an initiation criterion. Both drugs would have the same place of therapy in the population for this indication.
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.
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 an Investigator (Physician) Global Assessment score of 3 or 4. 2. Adequate control and refractory disease are optimally defined using similar criteria to those used in the dupilumab clinical trials, 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 be also considered for abrocitinib?	CDEC agreed with the clinical expert that these implementation considerations are relevant for the reimbursement of abrocitinib and should be noted in the recommendation.
Considerations for Continuation or Renewal of Therapy	
CDEC renewal criteria for dupilumab are 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 consideration be given to aligning the renewal criteria of abrocitinib with those recommended for dupilumab?	The clinical expert noted to CDEC that the renewal criteria are feasible to apply to abrocitinib, although the timing of 6 months (24 weeks) after initiation of treatment could be long for abrocitinib 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	
Should abrocitinib 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 abrocitinib. Appropriate specialists would include a pediatric dermatologist, a general dermatologist or a pediatrician with an interest in AD.
Can abrocitinib be used in combination with other JAK inhibitors, biologic DMARDs, phototherapy, or immunosuppressants?	CDEC agreed with the clinical expert that abrocitinib should not be used in combination with other systemic treatments for AD (there is no evidence investigating the safety and efficacy of such combinations).
Generalizability	
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 has 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 abrocitinib in the treatment of AD.

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

The evidence for this review was derived from a systematic literature review of pivotal and phase III studies that was supplemented with additional studies to address important gaps in the evidence from RCTs. The systematic review included 6 double-blind, phase III, RCTs: two 12-week placebo-controlled trials conducted with abrocitinib as monotherapy for AD (JADE MONO-1 [N = 387] and JADE MONO-2 [N = 391]); 2 placebo-controlled trials conducted with abrocitinib as combination therapy for AD (JADE COMPARE [N = 838 adults] and JADE TEEN [N = 287 adolescents]); one 26-week active-controlled trial comparing abrocitinib and dupilumab as combination therapy (JADE DARE [N = 727]); and 1 placebo-controlled, responder-enriched, withdrawal trial (JADE REGIMEN [N = 789]). The evidence from these studies was supplemented with the interim results from 1 long-term extension phase study (JADE EXTEND) and 3 ITCs.

The included studies evaluated a range of outcomes that are important in the management of AD, including overall severity of AD (e.g., Eczema Area and Severity Index [EASI] and Investigator's Global Assessment [IGA]), severity of itching (e.g., severity of peak pruritus numerical rating scale [PP-NRS]), symptoms (e.g., Patient-Oriented Eczema Measure [POEM] and Pruritus and Symptoms Assessment for Atopic Dermatitis [PSAAD]), HRQoL (e.g., DLQI and CDLQI), fatigue (e.g., Functional Assessment of Chronic Illness Therapy Fatigue Scale [FACIT-F]), patient-reported anxiety and depression, and the need for additional AD medications (e.g., corticosteroid-free days). In addition, the JADE REGIMEN study investigated the use of abrocitinib (100 mg once daily or 200 mg once daily) as a maintenance therapy for patients who achieved an initial response to the abrocitinib 200 mg once daily dosage

regimen by evaluating time to acute worsening of the patient's condition (i.e., development of a disease flare in accordance with standardized criteria).

The eligibility criteria for the included RCTs were similar except for the differences in the age ranges for the combination therapy studies (i.e., JADE COMPARE and JADE DARE were limited to adults and JADE TEEN was limited to adolescents) and the need to establish a response to abrocitinib 200 mg once daily to be randomized in JADE REGIMEN. All of the trials enrolled patients with moderate to severe AD and an inadequate response to topical AD therapies. This is reflective of the indication that was initially submitted to Health Canada and CADTH; however, the approved indication reflects a more restrictive population (i.e., those with refractory moderate to severe AD and an inadequate response to other systemic drugs). The proportion of patients with prior exposure to at least 1 systemic therapy for AD in the included trials was: 48.3% in JADE MONO-1, 41.4% in JADE MONO-2, 43.2% in JADE COMPARE, 47.9% in JADE DARE, 25.6% in JADE TEEN, and 59.5% (in both the open-label induction phase and the double-blind treatment phase) in JADE REGIMEN.

Efficacy Results

In the active-controlled, combination therapy trial (JADE DARE), treatment with abrocitinib 200 mg once daily was superior to dupilumab once every 2 weeks for demonstrating EASI-90 and IGA responses in the initial 20 weeks after starting treatment, but there were no statistically significant differences between the 2 drugs at 26 weeks.

When used as monotherapy and combination therapy, abrocitinib 100 mg once daily and 200 mg once daily resulted in statistically significant increases in the proportion of patients who demonstrated EASI-75 and IGA responses at 12 weeks compared with placebo (i.e., the co-primary end points). The adjusted differences for abrocitinib 100 mg once daily and 200 mg once daily (respectively) compared with placebo for EASI-75 response in each study were: JADE MONO-1 (27.9% [95% CI, 17.4 to 38.3; P < 0.0001] and 51.0% [95% CI, 40.5 to 61.5; P < 0.0001]), JADE MONO-2 (33.9% [95% CI, 23.3 to 44.4; P < 0.0001] and 50.5% [95% CI, 40.0 to 60.9; P < 0.0001]), JADE COMPARE (31.9% [95% CI, 22.2 to 41.6; P < 0.0001] and 43.2% [95% CI, 33.7 to 52.7; P < 0.0001]), and JADE TEEN (26.5% [95% CI, 13.1 to 39.8; P = 0.0002] and 29.4% [95% CI, 16.3 to 42.5; P < 0.0001]). Similar results were demonstrated for IGA response at 12 weeks compared with placebo: JADE MONO-1 (15.8% [95% CI, 6.8 to 24.8; P = 0.0037] and 36.0% [95% CI, 26.2 to 45.7; P < 0.0001]), JADE MONO-2 (19.3% [95% CI, 9.6 to 29.0; P = 0.0008] and 28.7% [95% CI, 18.6 to 38.8; P < 0.0001]), JADE COMPARE (23.1% [95% CI, 14.7 to 31.4; P < 0.0001] and 34.8% [95% CI, 26.1 to 43.5; P < 0.0001]), and JADE TEEN (16.7% [95% CI, 3.5 to 29.9; P = 0.0147] and 20.6% [95% CI, 7.3 to 33.9; P = 0.0030]). The clinical expert consulted by CADTH noted that the results for EASI-75 and IGA response compared with placebo are clinically meaningful.

In the subgroup of patients with prior use of a systemic immunosuppressant for AD, the adjusted differences for abrocitinib 100 mg once daily and 200 mg once daily (respectively) compared with placebo for IGA response were: JADE MONO-1 (9.1% [95% CI, −1.2 to 19.4] and 36.2% [95% CI, 22.7 to 49.7]), JADE MONO-2 (20.4% [95% CI, 6.7 to 34.1] and 26.9% [95% CI, 12.1 to 41.6]), JADE COMPARE (27.5% [95% CI, 14.4 to 40.6] and 43.9% [95% CI, 30.7 to 57.1]), and JADE TEEN (18.6% [95% CI, −1.7 to 38.9] and 41.7% [95% CI, 18.0 to 65.3]). For EASI-75 response, the adjusted differences for abrocitinib 100 mg once daily and 200 mg once daily (respectively) compared with placebo for IGA response were: JADE MONO-1 (17.0% [95% CI, 2.6 to 31.4]) and 49.3% [95% CI, 33.8 to 64.7]), JADE MONO-2 (30.9% [95% CI, 16.4 to 45.3] and 54.6% [95% CI, 39.4 to 69.7]), JADE COMPARE (49.1% [95% CI, 35.5 to 62.7]

and 63.0% [95% CI, 50.3 to 75.7]), and JADE TEEN (24.7% [95% CI, −1.7 to 51.1] and 39.0% [95% CI, 12.4 to 65.7]).

A statistically significantly greater proportion of patients in both the abrocitinib groups demonstrated an EASI-90 response at 12 weeks in JADE MONO-1, JADE MONO-2, and JADE TEEN, and at 16 weeks in JADE COMPARE. Similarly, a statistically significantly greater proportion of patients in both the abrocitinib groups demonstrated an EASI-100 response at 12 weeks in JADE MONO-1 and JADE MONO-2, and at 16 weeks in JADE COMPARE. There was no statistically significant difference between the abrocitinib and placebo groups for EASI-100 response in JADE TEEN.

Patient groups and the clinical expert consulted by CADTH identified itch as the most burdensome symptom of AD. In both the monotherapy and combination therapy trials, both doses of abrocitinib demonstrated that a greater proportion of patients achieved PP-NRS4 response. The adjusted differences for abrocitinib 100 mg once daily and 200 mg once daily (respectively) compared with placebo for PP-NRS4 response in each study were: JADE MONO-1 (least squares mean difference [LSMD]: 22.5% [95% CI, 10.3 to 34.8; P = 0.0003] and 41.7% [95% CI, 29.6 to 53.9; P < 0.0001]), JADE MONO-2 (LSMD: 33.7% [95% CI, 22.8 to 44.7; P < 0.0001] and 43.9 [95% CI, 32.9 to 55.0; P < 0.0001]), JADE COMPARE (18.1% [95% CI, 6.2 to 30.0; P = 0.0045] and 32.7% [95% CI, 21.0 to 44.4; P < 0.0001] at 16 weeks), JADE TEEN (22.8% [95% CI, 8.0 to 37.7; P = 0.0035] and 25.6% [95% CI, 10.6 to 40.6; P = 0.0013] at 12 weeks). The results were statistically significant for all comparisons with the exception of the JADE TEEN trial (due to failure of the statistical testing hierarchy at a higher order end point [i.e., PP-NRS4 at 4 weeks for the abrocitinib 100 mg group]) and were considered to be clinically meaningful by the expert consulted by CADTH. No subgroup analyses were performed for PP-NRS4 response in the placebo-controlled trials. In JADE DARE, for the co-primary end point of PP-NRS4 at week 2, abrocitinib 200 mg once daily was superior to dupilumab 300 mg once every 2 weeks (48.2% versus 25.5%; 22.6% [95% CI, 15.8 to 29.5; P < 0.0001]). The difference between groups for abrocitinib 200 mg once daily versus dupilumab once every 2 weeks decreased over time and was similar between the 2 groups from week 12 onwards.

Those living with moderate to severe AD can experience sleep disruption due to the symptoms of their condition, particularly the persistent itch. Both 100 mg once daily and 200 mg once daily doses of abrocitinib resulted in statistically significant improvements in FACIT-F compared with placebo in JADE MONO-1 (LSMD: 3.6 [95% CI, 0.9 to 6.4; P = 0.0102] and 4.5 [95% CI, 1.8 to 7.3; P = 0.0013], respectively) and JADE MONO-2 (LSMD: 3.3 [95% CI, 0.8 to 5.9; P = 0.0107] and 4.3 [95% CI, 1.8 to 6.9; P = 0.0010], respectively). There was no statistically significant difference between either abrocitinib group and placebo for the smaller subset of adolescent patients who completed the Peds-FACIT-F. In the combination therapy trials, the FACIT-F scale was not evaluated in the JADE COMPARE trial and there was no statistically significant difference between either dose of abrocitinib and placebo in the Peds-FACIT-F in the JADE TEEN study. No subgroup analyses were performed for FACIT-F and Peds-FACIT-F.

Patient groups and the clinical expert consulted by CADTH reported that AD can have a profound negative impact on the mental well-being of those living with the condition and they are at risk of experiencing depression. The monotherapy studies and the combination therapy study in adults demonstrated that both 100 mg once daily and 200 mg once daily doses of abrocitinib resulted in statistically significant improvements in Hospital Anxiety and Depression Scale (HADS) anxiety scores and depression scores compared with placebo. There was no statistically significant difference in HADS between the abrocitinib and placebo

groups in JADE TEEN or the abrocitinib and dupilumab groups in JADE DARE. No subgroup analyses were performed for HADS.

Patient groups noted the importance of treatments that can improve quality of life for those living with moderate to severe AD. The included trials evaluated HRQoL using the DLQI and CDLQI instruments for adults and adolescents, respectively. Treatment with both abrocitinib 100 mg once daily and 200 mg once daily (respectively) was associated with a statistically significantly greater improvement (i.e., lower scores) in DLQI compared with placebo in JADE MONO-1 (LSMD: −2.8 [95% CI, −4.8 to −0.8; P = 0.0072] and −4.9 [95% CI, −6.9 to −2.9; P < 0.0001] at 12 weeks), JADE MONO-2 (LSMD: −4.4 [95% CI, −6.2 to −2.7; P < 0.0001] and −5.9 [95% CI, −7.7 to −4.2; P < 0.0001] at 12 weeks), and JADE COMPARE (LSMD: −2.8 [95% CI, −3.9 to −1.7; P < 0.0001] and −5.6 [95% CI, −6.7 to −4.5; P < 0.0001] at 16 weeks). Similarly, treatment with both abrocitinib 100 mg once daily and 200 mg once daily was associated with a statistically significantly greater improvement in CDLQI compared with placebo in JADE TEEN (LSMD: −2.3 [95% CI, −3.7 to −0.8; P = 0.0026] and −2.3 [95% CI, −3.8 to −0.9; P = 0.0018], respectively). For the adolescent subgroup of patients in the monotherapies, only the 200 mg once daily group demonstrated a statistically significant improvement in CDLQI compared with placebo. In JADE DARE, the change from baseline in DLQI was greater in the abrocitinib 200 mg group compared with the dupilumab treatment group from week 2 to week 20; however, the difference between the abrocitinib and dupilumab groups decreased overtime and was no longer statistically significant at 26 weeks. No subgroup analyses were performed for DLQI and CDLQI.

Treatment with both doses of abrocitinib typically resulted in statistically significant improvements in the additional secondary end points compared with placebo, including PSAAD, Scoring Atopic Dermatitis (SCORAD), POEM, Short Form-36 Version 2 (SF-36), and Patient Global Assessment (PtGA), although most of these end points were analyzed outside of the statistical testing hierarchy. JADE DARE demonstrated that abrocitinib was superior to dupilumab for improving SCORAD and POEM in the initial weeks after treatment initiation, but there were no statistically significant differences at week 26. No subgroup analyses were performed for these end points.

Exploratory analyses demonstrated that initiating treatment with the abrocitinib 200 mg once daily regimen was generally more efficacious than the 100 mg once daily regimen for establishing a response to treatment in the 12- to 16-week time frame that was studied in the phase III clinical trials. The clinical expert consulted by CADTH noted that specialists are likely to initiate treatment with the higher dosage for most patients and then may consider reducing the dosage based on the patient's response to therapy and/or tolerability. This approach for reducing the 200 mg dosage is aligned with the dosing recommendations in the product monograph (i.e., for patients using the 200 mg once daily dosage, after symptom control is achieved, consider dose reduction to 100 mg once daily).

Harms Results

Abrocitinib 100 mg once daily and 200 mg once daily were generally well tolerated with few serious adverse events (SAEs) or withdrawals due to adverse events (WDAEs) for up to 16 weeks in the phase III trials and 48 weeks in the interim analysis of the long-term extension phase study (JADE EXTEND). No subgroup analyses based on prior exposure to at least 1 systemic therapy for AD were performed for adverse events.

In the monotherapy studies (JADE MONO-1 and JADE MONO-2), the proportion of patients who had at least 1 adverse event (AE) was greater in the abrocitinib 100 mg once daily (69.2% and 62.7%) and 200 mg groups (77.9% and 65.8%) compared with the placebo groups (57.1% and 53.8%). Nausea, headache, and acne occurred in at least 5% more patients treated with abrocitinib than those in the placebo group. The proportion of patients with at least 1 SAE was similar between abrocitinib groups (3.2% in both) and the placebo group (3.9%) in JADE MONO-1. In JADE MONO-2, the proportion with at least 1 SAE was 3.2% in the abrocitinib 100 mg once daily group, 1.3% in the abrocitinib 200 mg once daily group, and 1.3% in the placebo group. In JADE MONO-1, the proportion of patients who withdrew because of AEs was 9.1% in the placebo group, 5.8% in the abrocitinib 100 mg once daily group, and 5.8% in the abrocitinib 200 mg once daily group. In JADE MONO-2, the proportion of patients who withdrew because of AEs was 12.8% in the placebo group, 3.8% in the abrocitinib 100 mg once daily group, and 3.2% in the abrocitinib 200 mg once daily group. WDAEs included events categorized as worsening AD, which contributed to the high proportion of withdrawal within the placebo groups of the monotherapy studies. Serious infections and opportunistic infections were rare in the monotherapy studies. Blood creatine phosphokinase (CPK) elevation was reported for more patients in abrocitinib groups compared with placebo. There were no malignancies, major adverse cardiovascular events (MACEs), or VTE events reported during the trials.

When used as combination therapy in adults, the proportion of patients who had at least 1 treatment-emergent AE was greater in the abrocitinib 200 mg group (61.9%) compared to the abrocitinib 100 mg (50.8%), dupilumab 300 mg every 2 weeks (50.0%), and placebo (53.4%) groups in JADE COMPARE. In JADE DARE, the proportion of patients who had at least 1 treatment-emergent AE was greater in the abrocitinib 200 mg group (74.0%) compared to the dupilumab 300 mg every 2 weeks group (65.5%). Most events were mild or moderate in severity in both JADE COMPARE and JADE DARE. Nausea, headache, and acne were the most reported AEs in the abrocitinib groups and conjunctivitis was the most frequent in the dupilumab group. The proportion of patients with at least 1 SAE was 3.8% in the placebo group, 2.5% in the abrocitinib 100 mg once daily group, 0.9% in the abrocitinib 200 mg group, and 0.8% in dupilumab group in JADE COMPARE, and 1.7% in the abrocitinib 200 mg group and 1.6% in the dupilumab group in JADE DARE. The proportion of patients who withdrew because of AEs was 3.8% in the placebo group, 2.5% in the abrocitinib 100 mg once daily group, 4.4% in the abrocitinib 200 mg once daily group, and 3.3% in the dupilumab group in JADE COMPARE, and 3.3% in the abrocitinib 200 mg once daily group and 2.5% in the dupilumab group in JADE DARE.

When used as combination therapy in adolescents (JADE TEEN), the proportion of patients who had at least 1 AE was greater in the abrocitinib 200 mg once daily group (62.8%) compared to the abrocitinib 100 mg once daily (56.8%) and placebo (52.1%) groups. Nausea and acne were more commonly reported with abrocitinib compared with placebo. There were 2 SAEs reported in the placebo group and 1 SAE reported in the abrocitinib 200 mg once daily group. The proportion of patients who withdrew because of AEs was 2.1% in the placebo group, 1.1% in the abrocitinib 100 mg once daily group, and 2.1% in the abrocitinib 200 mg once daily group.

Serious infections and opportunistic infections were rare in the combination therapy studies. Herpes zoster and blood CPK elevations were reported for more patients in the abrocitinib groups compared with the placebo group in both JADE COMPARE and JADE TEEN. There were no malignancies, MACEs, or VTE events reported during the trials for patients treated with abrocitinib (a malignancy was reported for 1 patient treated with dupilumab in JADE COMPARE).

Critical Appraisal

Randomization was stratified based on relevant prognostic factors in JADE MONO-1, JADE MONO-2, and JADE TEEN (i.e., baseline AD severity [moderate or severe] in all 3 studies and age [< 18 years or ≥ 18 years] in JADE MONO-1 and JADE MONO-2). There was no stratification at the time of randomization in JADE COMPARE, stratification based only on age (< 18 years or ≥ 18 years) in JADE REGIMEN, and stratification based on disease baseline AD severity in JADE DARE. The baseline and demographic characteristics were generally well balanced across the treatments of each of the studies. The study treatments were administered in a double-blind manner and a double-dummy design was used to maintain blinding in the JADE COMPARE and JADE DARE trials to account for the oral administration of abrocitinib and the subcutaneous injection for dupilumab. The AE profile of abrocitinib and the comparators (placebo or dupilumab) was unlikely to compromise blinding in any of the included trials. As the trials were placebo-controlled, it is possible that some patients could infer their allocated treatment assignment due to improvement or lack of improvement in AD over the study period, as well as the use of rescue medication, which occurred in a higher proportion of patients in the placebo groups of the included studies. WDAEs included events categorized as worsening AD, which contributed to the high proportion of withdrawal within the placebo groups of the monotherapy studies. Adherence to the study treatments was evaluated by counting the number of study drugs at each visit and median compliance was 100% across all treatment groups. There were few patients who discontinued from the combination therapy trials (completion rates ranged from 89.3% to 96.8% across the treatment groups), but the completion rates were considerably lower in the placebo groups of the monotherapy trials (79.2% and 66.7% in JADE MONO-1 and JADE MONO-2, respectively) compared with the abrocitinib groups (range = 86.5% to 91.0%). True intention-to-treat analyses were not performed; however, the full analysis sets included nearly all randomized patients, and sensitivity analyses were performed to investigate the impact of missing data. Missing data were more common in the placebo arms of the studies and may have biased the results in favour of the active treatments, as analysis approaches and imputation of missing data assumed the data were missing at random (e.g., missing data imputed as a non-responder); however, numerous sensitivities analyses were performed to investigate the impact of missing data, and results remained robust.

All end points within the statistical testing hierarchies were statistically significant in JADE MONO-1, JADE MONO-2, JADE COMPARE, and JADE DARE. The statistical testing hierarchy was stopped at the first key secondary end point of JADE TEEN (i.e., PP-NRS4 response); however, the sponsor continued to calculate and report P values for the remaining key secondary end point (i.e., nominal P values were considered to be descriptive). Subgroup analyses, secondary end points, and exploratory end points were tested without adjustment for multiple comparisons, and all P values are considered nominal. Subgroup analyses for patients with prior exposure to at least 1 systemic therapy for AD were limited to the primary and key secondary end points (e.g., IGA response and EASI-75 response). There were imbalances in baseline disease severity across the treatment groups in the subgroup analyses based on prior exposure to at least 1 systemic therapy for AD. Overall, the clinical expert consulted by CADTH indicated that these analyses suggested that the response to abrocitinib would likely be similar for those with and without prior exposure to a systemic therapy for AD.

The diagnostic criteria used in the screening process for the included studies were consistent with Canadian clinical practice for identifying patients with moderate to severe AD. Overall, the clinical expert consulted by CADTH indicated that the populations enrolled

in the included trials were a reasonable reflection of the target population in Canada. The clinical expert consulted by CADTH noted that the co-primary end points (EASI and IGA) are clinically relevant and can be evaluated in routine Canadian practice for determining response to treatment with abrocitinib (i.e., for the purposes of establishing renewal criteria for reimbursement by the public drug programs).

AD is a chronic disease and abrocitinib would likely be used as a long-term treatment for patients who require systemic therapy. The placebo-controlled trials were short-term (12 and 16 weeks) with only limited data available from the longer-term studies (JADE EXTEND and JADE REGIMEN) at the time this review. Complete reporting of the longer-term studies will help characterize the longer-term efficacy and safety of abrocitinib in the treatment of AD.

Indirect Comparisons

Description of Studies

CADTH summarized and appraised 3 ITCs: 2 unpublished ITCs submitted by the sponsor (one network meta-analysis [NMA] and 1 matched-adjusted indirect comparison [MAIC]) and a published ITC by the Institute for Clinical and Economic Review. The NMAs compared abrocitinib against dupilumab, upadacitinib, and tralokinumab, and several drugs that were not listed as under review by Health Canada or CADTH at the time of this review (e.g., nemolizumab, lebrikizumab, and baricitinib). The MAIC compared abrocitinib 100 mg once daily and 200 mg once daily against cyclosporine and methotrexate (2 drugs that are not approved by Health Canada for use as systemic treatments for AD but are commonly used in Canada).

Efficacy Results

Population With Prior Exposure to a Systemic Therapy for AD (Subgroup Analysis From Sponsor's NMA)

Subgroup analyses for patients reporting AD treatment failure with systemic immunosuppressants before study enrolment were limited to IGA response and EASI-75 for the monotherapy studies. Comparisons could only be conducted for abrocitinib 100 mg once daily, abrocitinib 200 mg once daily, dupilumab 200 mg or 300 mg once every 2 weeks, and placebo. The odds ratios for IGA response were: abrocitinib 200 mg once daily versus placebo ([redacted]), abrocitinib 200 mg once daily versus dupilumab 200 mg or 300 mg once every 2 weeks ([redacted]), and abrocitinib 200 mg once daily versus abrocitinib 100 mg once daily ([redacted]). The odds ratios for EASI-75 response were: abrocitinib 200 mg once daily versus placebo ([redacted]), abrocitinib 200 mg once daily versus dupilumab 200 mg or 300 mg once every 2 weeks ([redacted]), abrocitinib 200 mg once daily versus dupilumab 300 mg once every 2 weeks ([redacted]), and abrocitinib 200 mg once daily versus abrocitinib 100 mg once daily ([redacted]).

Subgroup analyses for patients reporting AD treatment failure with systemic immunosuppressants before study enrolment were limited to a single composite end point (EASI-50 plus DLQI improvement of ≥ 4 points) in the combination therapy NMA. Comparisons could only be conducted for abrocitinib 100 mg once daily, abrocitinib 200 mg once daily, dupilumab 300 mg once every 2 weeks, and placebo. The odds ratios for achieving an EASI-50 response and a DLQI improvement of 4 points or greater were: abrocitinib 200 mg once daily versus placebo ([redacted]), abrocitinib 200 mg once daily versus dupilumab 300 mg once every 2 weeks ([redacted]), and abrocitinib 200 mg once daily versus abrocitinib 100 mg once daily ([redacted]).

Overall Population

The sponsor NMA reported that abrocitinib 200 mg once daily, upadacitinib 30 mg and 15 mg once daily, and dupilumab 300 mg once every 2 weeks [redacted]. Based on improvements in EASI, abrocitinib 200 mg once daily was [redacted] when these treatments were used as monotherapy. When used in combination with topical therapies, abrocitinib 200 mg once daily was [redacted]. The Institute for Clinical and Economic Review NMA results were generally similar to those reported by the sponsor with respect to the comparative efficacy of abrocitinib 200 mg once daily. The sponsor NMA did not compare abrocitinib 100 mg once daily against all of the comparators (only placebo). However, the Institute for Clinical and Economic Review NMA reported that, for most efficacy outcomes, abrocitinib 100 mg was either inferior or occasionally comparable to upadacitinib (30 mg and 15 mg once daily), abrocitinib 200 mg once daily, and dupilumab 300 mg once every 2 weeks, while it was superior (or occasionally comparable) to tralokinumab 300 mg once every 2 weeks and placebo.

The sponsor-submitted MAIC reported that abrocitinib at both 100 mg once daily and 200 mg once daily doses [redacted] than cyclosporine and methotrexate.

Harms Results

In the NMAs, treatment-emergent AEs and discontinuations due to AEs were [redacted]. The sponsor-submitted MAIC reported that abrocitinib at both 100 mg once daily and 200 mg once daily doses [redacted] when compared to cyclosporine and methotrexate. There were no subgroup analyses conducted for the AE end points.

Critical Appraisal

Subgroup analyses for patients reporting AD treatment failure with systemic immunosuppressants before study enrolment were limited to IGA response and EASI-75 for the monotherapy NMAs, and a single composite end point (EASI-50 plus DLQI improvement of ≥ 4 points) in the combination therapy NMAs. Due to the small number of patients in the LIBERTY AD ADOL trial with prior exposure to at least 1 systemic therapy for AD (n = 11 for the dupilumab 200 mg or 300 mg once every 2 weeks group and n = 9 the placebo group), there was considerable uncertainty in the estimates of effect for the monotherapy NMA for IGA response. Similar to the primary NMA analyses, [redacted].

The sponsor-submitted NMA did not report on the comparative efficacy and safety of abrocitinib 100 mg when compared with other treatments. Most importantly, conclusions regarding the long-term efficacy of abrocitinib 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 some of the findings; hence, results from the sponsor-submitted ITC must be interpreted with caution. The conclusion for the MAIC must be weighed against the highly unstable nature of unanchored indirect comparisons that, while being improvements on naive comparisons, are still highly prone to potential biases. Until direct evidence is available, the efficacy and safety differences between abrocitinib and cyclosporine/methotrexate will remain inconclusive.

Other Relevant Evidence

Description of Studies

JADE EXTEND is an ongoing multi-centre, quadruple-masked, randomized phase III study for evaluating the long-term efficacy and safety of abrocitinib, with or without topical medications, in patients aged 12 years and older with moderate to severe AD. Patients who complete the JADE MONO-1, JADE MONO-2, JADE COMPARE, JADE TEEN, and JADE REGIMEN studies are eligible for enrolment in JADE EXTEND. Only limited data for patients from JADE MONO-1 and JADE MONO-2 were available at the time of the CADTH review. Patients in JADE EXTEND remained on the same dose of abrocitinib that they received in the parent study and patients in the placebo groups of the parent study were re-randomized to treatment with abrocitinib 100 mg once daily or 200 mg once daily. The end points reported for JADE EXTEND included IGA, EASI-75, and PP-NRS4 response.

At the data cut-off for the interim analysis (April 22, 2020), 520 eligible patients that participated in JADE MONO-1 and JADE MONO-2 were included in JADE EXTEND. Abrocitinib monotherapy was maintained in 361 of 520 patients in JADE EXTEND, while 159 patients received combination therapy of abrocitinib and topical medication. Approximately 25% of patients in both the 100 mg once daily and 200 mg once daily abrocitinib groups had discontinued from JADE EXTEND by week 48.

Efficacy Results

The sponsor reported interim results for 48 weeks of treatment for patients who completed the JADE MONO-1 or JADE MONO-2 trials. IGA response rate increased from 26.0% to 45.2% in the abrocitinib 100 mg once daily group and 40.9% to 60.5% in the abrocitinib 200 mg once daily group between week 12 and week 48 of treatment. EASI-75 response rate increased from 42.1% to 68.0% in the abrocitinib 100 mg once daily group and 61.9% to 87.2% in the abrocitinib 200 mg once daily group between week 12 and week 48 of treatment. PP-NRS4 response rate increased from 41.6% to 52.0% in the abrocitinib 100 mg once daily group and 56.3% to 72.5% in the abrocitinib 200 mg once daily group between week 12 and week 48 of treatment.

The clinical expert consulted by CADTH noted that an important gap in the phase III evidence base is the use of abrocitinib in patients who experienced an inadequate response or whose condition is no longer controlled by treatment with dupilumab. As such, CADTH included the information available for this subgroup of patients from JADE EXTEND. The sponsor reported exploratory analyses to evaluate the efficacy of 12 weeks of abrocitinib treatment in patients who were previously treated with dupilumab for 16 weeks in JADE COMPARE and failed to demonstrate an IGA response, EASI-75 response, and PP-NRS4 responses. Further subgroup analyses were conducted for primary non-responders (defined as patients who did not achieve response at any visit through week 16 of JADE COMPARE) and secondary non-responders (defined as patients who had achieved a response at any time before week 16 but were non-responders at week 16). IGA responses were reported for 34.3% and 47.2% of dupilumab non-responders who received 12 weeks of abrocitinib 100 once daily and abrocitinib 200 once daily, respectively. EASI-75 responses were reported for 67.7% and 80.0% of dupilumab non-responders who received 12 weeks of abrocitinib 100 once daily and abrocitinib 200 once daily, respectively. PP-NRS4 responses were reported for 37.8% and 81.0% of dupilumab non-responders who received 12 weeks of abrocitinib 100 once daily and abrocitinib 200 once daily, respectively.

Harms Results

There were no harms data reported for JADE EXTEND at the time of the submission to CADTH.

Critical Appraisal

JADE EXTEND is an ongoing double-blind extension study that enrolled patients from the phase III RCTs. Only interim data were available at the time of the submission to CADTH, and reporting was limited to an interim analysis with partial reporting (i.e., a clinical study report was not available to enable a fulsome appraisal). Extension studies are often limited by selection bias, as only patients who are tolerant to treatment and complete the parent studies are eligible to enrol. At the time of interim analysis, there was a large proportion of patients who had withdrawn from both the abrocitinib 100 mg once daily (22.9%) and abrocitinib 200 mg once daily (20.0%) groups at 48 weeks. Issues with the generalizability of these data are the same as for the parent double-blind studies. Patients were considered to be dupilumab non-responders if they failed to demonstrate an IGA response, EASI 75 response, and PP-NRS4 responses after 16 weeks of treatment; a time period that was likely insufficient to fully realize the maximal treatment effects for dupilumab. The CADTH reimbursement recommendation for dupilumab for patients aged 12 years and older with moderate to severe AD indicates that the response to treatment should be evaluated after 6 months of treatment.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree/Markov model hybrid
Target population	Adults and adolescents (≥ 12 years) with moderate to severe AD who have had an inadequate response to prescribed topical therapies, or for whom these treatments are not advisable; patients are assumed to have had no prior use of immunosuppressants (IMMs)
Treatments	ABRO 100 mg + SoC ABRO 200 mg + SoC
Submitted price	ABRO, 50 mg, 100 mg: $48.67 per tablet ABRO, 200 mg: $54.47 per tablet
Annual treatment cost	ABRO 100: $17,765 ABRO 200: $19,882
Comparators	SoC (comprised of a basket of topical corticosteroids, topical calcineurin inhibitors, phosphodiesterase type 4 inhibitors, oral antihistamines) DUP + SoC CYC + SoC MTX + SoC
Perspective	Canadian publicly funded health care payer

Component	Description
Outcome	QALYs
Time horizon	Lifetime (up to patient age 110 years)
Key data source	Treatment inputs for ABRO were informed by JADE COMPARE, JADE EXTEND, JADE MONO-1, JADE MONO-2, JADE TEEN, and JADE DARE. A network meta-analysis was used to compare effectiveness of ABRO vs. DUP and SoC; comparative effectiveness for MTX and CYC was based on an unanchored MAIC.
Key limitations	• The pharmacoeconomic evaluation of ABRO may not reflect its clinical use in the following aspects: 1) the target population of the sponsor's base case (patients eligible for systemic IMMs) is not aligned with the indication or the anticipated place of ABRO in therapy (among those refractory or ineligible for IMMs); 2) the clinical expert consulted by CADTH for this review indicated that most patients will start treatment on ABRO 200, potentially stepping down to ABRO 100 depending on treatment response and adverse events. • Treatment adherence, which would be expected to impact both costs and health outcomes, is not considered in the sponsor's model. Clinical expert feedback suggested that adherence would be lower among patients taking ABRO compared to DUP, owing to the mode of administration. • Relevant comparators, such as some IMMs, retinoids, and phototherapy were not considered. Additionally, the comparative effectiveness data from the sponsor's MAIC for methotrexate and cyclosporine is highly uncertain. • The use of clinical effectiveness data assessed at 16 weeks of treatment may overestimate the incremental effectiveness of ABRO compared with DUP, owing to a longer onset of effect for DUP. The use of 16-week outcome data may bias the ICER in favour of ABRO. • The health state utility values adopted by the sponsor are highly uncertain and lacked face validity. • The long-term efficacy of ABRO is unknown. Treatment discontinuation and effectiveness waning for ABRO, both influential factors in the economic analysis, were based on assumptions that were not supported by trial data. • The sponsor assumed that the impact of adverse events would be captured by health state utility values. The model did not include all adverse events deemed important by clinical experts consulted for this review. The utility measure chosen for the analysis likely does not capture health changes due to adverse events identified by patients and the clinical expert as being highly relevant. • The cost-effectiveness of ABRO in an adolescent population is uncertain. The sponsor's model assumed a cohort starting age of 29 years. The sponsor's NMA was based on adult patients, and assumptions were required about the relative effectiveness of treatments among adolescents. Treatment adherence, which was not considered in the model, may vary between adults and adolescents. • The sponsor's model employed poor modelling practices, preventing CADTH from fully validating the model and its findings.
CADTH reanalysis results	• CADTH reanalyses included: assuming that ABRO will be used by patients who are refractory or ineligible for systemic IMMs, removing MTX and CYC as comparators; assuming that health state utility values are equal, regardless of which treatment is received; assuming the utility benefit for treatment response starts at 8 weeks for all treatments; and assuming that treatment effectiveness will wane over the entire analysis horizon. • CADTH was unable to address the lack of comparative clinical effectiveness data for some relevant treatment comparators, the impact of treatment adherence and adverse events, and the lack of long-term treatment efficacy data beyond 52 weeks. The comparative effectiveness of all comparators is highly uncertain beyond 16 weeks. Consequently, the results of the economic analysis are highly uncertain. CADTH noted that the results are highly dependent on the price of DUP. CADTH was additionally unable to address the cost-effectiveness of ABRO among patients who have had an inadequate response to biologics.

Component	Description
	• The estimated ICERs from the CADTH reanalysis were higher than those submitted by the sponsor: ◦ Patients refractory or ineligible for systemic IMMs: ▪ ABRO 100 + SoC vs. SoC = $156,735 per QALY ▪ ABRO 200 + SoC vs. ABRO 100 + SoC = $231,013 per QALY • A key scenario analysis was conducted to reflect clinical practice as anticipated by clinical experts, who suggested that adult patients would initiate treatment with ABRO 200. In patients with refractory or ineligible for systemic IMMs, where ABRO 100 + SoC was removed from the analysis, the ICER for ABRO 200 + SoC compared to SoC is $177,248 per QALY (DUP was dominated by ABRO 200 + SoC).

ABRO = abrocitinib; AD = atopic dermatitis; CYC = cyclosporine; DUP = dupilumab; ICER = incremental cost-effectiveness ratio; IMM = immunosuppressant; MAIC = matched-adjusted indirect comparison; MTX = methotrexate; QALY = quality-adjusted life-year; SoC = standard of care.

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 abrocitinib; the number of individuals eligible for public drug plan coverage are underestimated; there is uncertainty in the proportion of patients prescribed abrocitinib 100 versus abrocitinib 200; there is uncertainty in adherence rate to oral treatments (abrocitinib, cyclosporine, and methotrexate) and subcutaneous injection (dupilumab); there is high uncertainty in the incidence rates of AD; and the proportion of patients who receive treatment is overestimated. CADTH reanalysis included using the proportion of patients eligible for coverage to calculate market size.

Based on CADTH reanalyses, the budget impact to the public drug plans of introducing abrocitinib for patients with moderate to severe AD who are refractory or ineligible for systemic immunomodulators is expected to be a cost savings of $790,027 in year 1, $9,693,656 in year 2, and $39,556,691 in year 3, for a 3-year estimated savings of $50,040,374. The estimated budget impact is sensitive to the proportion of patients who are eligible for public drug plan coverage, assumptions around market share distribution, adherence rates, and the proportion of patients receiving a systemic immunosuppressant.

CDEC Information

Members of the Committee

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

Meeting Date: May 26, 2022

Regrets: One expert committee member did not attend

Conflicts of Interest: None