Canada's Drug Agency
L'Agence des médicaments du Canada

Reimbursement Recommendation

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(Draft)

Ruxolitinib (Opzelura)

Indication: For the topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with conventional topical prescription therapies (topical corticosteroids, topical calcineurin inhibitors) or when those therapies are not advisable

Sponsor: Incyte Biosciences Canada Corporation

Recommendation: Do Not Reimburse

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Recommendation

The CDA-AMC Canadian Drug Expert Committee (CDEC) recommends that ruxolitinib 1.5% cream not be reimbursed for the topical treatment of mild to moderate atopic dermatitis (AD) in adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with conventional topical prescription therapies (topical corticosteroids [TCS], topical calcineurin inhibitors [TCI]) or when those therapies are not advisable.

Rationale for the Recommendation

CDEC acknowledged the potential need for additional treatment options that effectively reduce the severity and symptoms of AD and are safe; however, CDEC identified several limitations and uncertainties in the submitted evidence that did not allow the committee to determine whether ruxolitinib 1.5% cream will provide clinically meaningful benefit in the patient population under review.

Evidence for ruxolitinib cream was reviewed based on the Health Canada indication, which limits usage to patients with mild to moderate AD whose disease is not adequately controlled with TCS and/or TCI, and those who are not candidates for those treatments. However, the 2 double-masked, randomized, vehicle-controlled trials (TRuE-AD1, N = 631; TRuE-AD2, N = 618) enrolled patients who had mild to moderate AD without restricting trial entry based on response to prior TCS and/or TCI treatments. Although the results of the pivotal trials suggested added clinical benefits with 8 weeks of ruxolitinib 1.5% cream treatment, compared to vehicle cream, in achieving Investigator Global Assessment-Treatment Success (IGA-TS) and Eczema Area and Severity Index 75 (EASI-75) response in patients 12 years of age and older with mild to moderate AD, the trial populations were not reflective of the anticipated use of ruxolitinib cream based on the indication under review. Post-hoc subgroup analyses in patients with recent history of TCS and/or TCI treatment were submitted as supporting evidence; however, the proportion of patients in the subgroup analyses that had inadequate response to TCS and/or TCI remains unknown. Additionally, the results of these post-hoc subgroup analyses were inconclusive due to methodological limitations, including a lack of sample size consideration and control for multiplicity.

There was a lack of direct comparative evidence for ruxolitinib cream versus active treatments used in Canada for the treatment of mild to moderate AD. Indirect comparative evidence submitted for review included 1 sponsor-submitted network meta-analysis (NMA), which assessed the efficacy of ruxolitinib 1.5% cream versus dupilumab, abrocitinib, and upadacitinib in patients with moderate AD. Results of this analysis were inconclusive due to imprecise results and important limitations that prevented verifying whether the underlying assumptions of homogeneity and consistency were met. Additionally, subgroup analyses in patents whose disease is not adequately controlled with, or who are not candidates for, TCS and/or TCI were not reported from the indirect treatment comparison (ITC). No comparative studies were submitted comparing ruxolitinib cream with off-label systemic immunosuppressants in patients with moderate AD. Overall, CDEC was unable to determine the comparative efficacy and safety of ruxolitinib 1.5% cream relative to currently available treatments for mild to moderate AD.

Patients identified a need for effective treatments that can reduce disease severity and the number of flares, improve quality of life, have fewer side effects, and offer a simplified treatment regimen by allowing topical application on multiple body areas including sensitive areas. Based on the evidence reviewed, CDEC concluded that ruxolitinib cream meets the need for an additional topical treatment option, but the committee could not determine whether ruxolitinib cream would adequately reduce disease severity and number of flares, improve quality of life, and have fewer side effects due to the uncertainties around the treatment effect of ruxolitinib cream compared to currently available treatments in the patient population under review.

Discussion Points

- **Lack of robust comparative evidence versus comparator treatments:** Although CDEC recognized the value that both patients and clinicians place in having a choice of treatment options for mild to moderate AD, the absence of robust comparative efficacy and safety data versus currently available treatments, specifically in patients who have inadequate response to TCS and/or TCI, preclude assessment of all factors necessary to balance all outcomes and unmet needs. The committee noted that there was no direct or indirect evidence in the patient population under review comparing the clinical benefits of ruxolitinib cream with other active therapies.
- **Limitations of the subgroup analyses:** CDEC discussed that the post-hoc subgroup analyses from the pivotal trials were conducted in patients who received TCS and/or TCI within 30 days prior to screening. Patients were included in these analyses regardless of response to prior TCS and/or TCI treatment and, therefore, the population included in the trials was not aligned with the patient population under review. Additionally, there is a lack of sample size consideration and control for multiplicity for these analyses. Given the methodological limitations and limited generalizability of the subgroup population, CDEC noted that no definitive conclusions could be drawn from the subgroup analyses.
- **Effects on health-related quality of Life (HRQoL) are uncertain:** CDEC discussed that there was evidence of low certainty from the TRuE-AD1 and TRuE-AD2 trials that ruxolitinib 1.5% cream may result in a clinically important improvement in dermatology-specific HRQoL in adults and little to no clinically important improvement in dermatology-specific HRQoL in adolescents at week 8, per Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessments. The clinical experts noted that it is plausible that the duration of follow-up at week 8 was insufficient for capturing the HRQoL effects of topical treatments in general, given that AD is a chronic condition that waxes and wanes over time. CDEC acknowledged this limitation of the dermatology-specific HRQoL analyses and noted that in addition, the analyses were associated with methodological limitations (differential dropouts between treatments groups and a risk of randomization not being fully preserved in the Children's Dermatology Life Quality Index [CDLQI] responder analysis). Additionally, the comparative HRQoL effects of ruxolitinib cream versus other active treatments for mild to moderate AD is unknown since HRQoL outcomes were not assessed in the sponsor-submitted NMA. Therefore, no definitive conclusions could be drawn on the clinical effects of ruxolitinib cream on HRQoL.
- **Long-term efficacy and safety are uncertain:** CDEC also considered results from the long-term safety (LTS) period of the pivotal trials, which suggested that the observed clinical benefits of ruxolitinib cream could potentially be sustained through 52 weeks and no notable safety concerns were identified. However, analyses beyond week 8 were noncomparative. Overall, no firm conclusion could be drawn on results of the LTS period due to the absence of a control group, potential risk of selection bias, and considerable loss to follow-up (approximately 20%) in both trials. Additionally, clinical expert input indicated that the duration of follow-up may be inadequate for capturing long-term safety of ruxolitinib cream, particularly for potentially rare adverse events (e.g., malignancies, major adverse cardiovascular events).

Background

AD is a chronic relapsing-remitting skin condition characterized by itching, inflammation, dryness, recurrent eczematous lesions, erythematous papules, and lichenification. The intense itch associated with AD could lead to sleep disturbances, mental health burden, and reduced quality of life in patients and caregivers. In Canada, the prevalence of AD is estimated to vary from 1.8% to 3.5% in adults and from 9.4% to 15.8% in adolescents. Currently available topical treatments for patients with mild to moderate AD included TCS and nonsteroidal topical treatments (TCIs and topical phosphodiesterase-4 inhibitor). Patients who do not achieve adequate disease control with topical treatments could receive phototherapy, off-label systemic immunosuppressant treatments (methotrexate, cyclosporine, mycophenolate mofetil, azathioprine), and advanced systemic therapies (e.g., dupilumab, upadacitinib, and abrocitinib). According to the clinical experts consulted by CDA-AMC, limitations of the currently available nonsteroidal topical treatments included poor efficacy in some patients and in body areas with thicker skin, potential application site reactions, difficult application for treatments in ointment formulation (tacrolimus), and high treatment costs.

Ruxolitinib 1.5% cream has been approved by Health Canada for topical treatment of mild to moderate AD in adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with conventional topical prescription therapies (TCS, TCI) or when those therapies are not advisable. Ruxolitinib is a Janus kinase inhibitor. It is available as a 1.5% topical cream and the dosage recommended in the product monograph is twice daily to affected skin areas up to a maximum of 20% of body surface area (BSA) for each application. Total BSA calculation excludes the scalp.

Sources of Information Used by the Committee

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

- a review of 2 phase III, double-masked, RCTs in adolescents and adults with mild to moderate AD, and their extension phase; 1 indirect treatment comparison study; and 1 phase II, open label, single-arm study
- patients' perspectives gathered by 3 patient groups, including input from the Eczema Society of Canada (ESC), and a joint input from the Canadian Skin Patient Alliance (CSPA) and Eczema Quebec (EQ)
- input from public drug plans that participate in the reimbursement review process
- Two clinical specialists with expertise diagnosing and treating patients with AD
- input from 2 clinician groups, including the Canadian Dermatology Association and the Atlantic Dermatology Specialist Group
- a review of the pharmacoeconomic model and report submitted by the sponsor

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups who responded to CDA-AMC's call for input and from clinical experts consulted by CDA-AMC for the purpose of this review. Note that the patient and clinician group inputs were received at the time of CDA-AMC's call for input based on the initial reimbursement request (i.e., for the topical treatment of AD in patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.), which predates the reimbursement request update provided by the sponsor (i.e., for the topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with conventional topical prescription therapies [TCS, TCI] or when those therapies are not advisable).

Patient Input

Two patient group inputs were submitted. The ESC is a registered Canadian charity with a mission of support, education, awareness, and research for people living eczema. ESC gathered information from more than 3,000 patients in Canada living with AD and their caregivers and/or family members via survey questionnaires and one-on-one interviews. Another patient group input was jointly submitted by the CSPA and EQ. The CSPA is a national non-profit organization that engages in collaboration, advocacy, and education for people affected by skin, hair, and nail conditions. EQ is a non-profit organization dedicated to providing support,

resources, and education to individuals and families affected by eczema in Quebec. The joint input was based on information gathered between February and October 2023 from various sources, including literature review, patients, 'The Skin I'm in' report, and in collaboration with an academic institution. Some patients (number not specified) surveyed by EQ indicated that they had experience with ruxolitinib cream treatment.

Both inputs highlighted that the signs and symptoms of AD, such as dry, itchy, inflamed skin that can lead to cracks, oozes, bleeds, and thickening of skin, affect many aspects of patients' lives such as physical, social, emotional, and professional aspects. Patients said itches can be extremely uncomfortable and painful, and requires frequent medical visits, specialized treatments, and ongoing care. Besides, the joint input by CSPA and EQ pointed out that AD is associated with other conditions such as asthma, seasonal allergies, environmental allergies, food intolerances, sleep disorders, anxiety, and depression. The inputs emphasized that caregivers and/or family members also share a significant burden of disease. The negative impact of AD on patients and their caregivers and/or families is amplified when AD is not well-controlled despite optimization of the treatment regimen, and when cycling through or switching to different therapies. Based on the input by ESC, uncontrolled AD or flares could lead to emergency department visits and hospitalizations. The input also highlighted that since AD can occur at a young age, it could cause significant impact on youth's performance at school, social life, and mental health. Based on the 2 inputs, patients expressed a need for new treatments that are safe, improve symptoms of AD, reduce flares, improve quality of life (e.g., better sleep quality, less psychological burden, able to carry out daily activities, establish and maintain intimate relationships), as well as reduce or eliminate potential complications and secondary infections associated with AD. Other key outcomes reported to be important to patients included fast and durable relief, reduced skin thickening, ease of medication use, and affordability. In addition, patients also value treatments that do not require injections. Patients expressed a need for treatments suitable for application on not only the body, but also the face and sensitive areas of the body, for a simplified regimen. The patient groups acknowledged that AD is a heterogeneous disease and requires a variety of treatments to fill gaps in therapeutic needs.

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

The clinical experts consulted for this review noted that currently available nonsteroidal topical treatments are not effective for all patients with AD and are inadequate for treating body areas with thick skin (e.g., palms and soles) or lichenification, associated with application site reactions (burning and stinging), and costly. As well, the clinical experts noted that a nonsteroidal topical treatment that is currently considered to be the most effective option (i.e., tacrolimus) is available in ointment formulation only, which is difficult to apply. One clinical expert anticipated that ruxolitinib would primarily serve as a second-line topical treatment following treatment failure with, or ineligibility to, TCS and/or TCI because of long-established treatment protocols favouring TCS and TCI, as well as anticipated access challenges for ruxolitinib cream due to higher drug cost relative to currently reimbursed topical treatments. The other clinical expert anticipated that ruxolitinib cream could also be used as a first-line topical treatment. This clinical expert further explained that TCIs are associated with application site reactions and moderate efficacy; provided that ruxolitinib cream is similarly or more effective and has fewer application site reactions than TCIs, the clinical expert thought it would be reasonable to use ruxolitinib cream ahead of TCIs, in particular for the face and groin for which TCS treatment is inappropriate. The clinical experts noted that determination of patients for whom use of TCS and TCI is advisable primarily depends on reaction to previous use (i.e., inadvisable in case of intolerance). According to the clinical experts, there are very few contraindications to TCS and TCI (e.g., the use of all TCS including hydrocortisone to the eyelids, long-term use of corticosteroids more potent than hydrocortisone to the face and intertriginous skin). In their experience, almost all topical treatment-naïve patients are eligible for TCS and TCI treatments. The clinical experts noted that depending on the severity of the symptoms and treatment response in each anatomical location, ruxolitinib cream could be used as either monotherapy or in combination with other topical therapies (applied to different affected areas). The clinical experts noted that when used concurrently with other topical therapies, ruxolitinib cream could be applied to the same or different anatomical locations; most patients are expected to use one treatment at a time in a given location and different topicals to different parts of the body.

One clinical expert noted that patients with AD who have facial or intertriginous involvement, inadequate response to or intolerable adverse events (AEs) from TCS and/or TCI treatments, and 10% or less body surface area (BSA) affected by AD, are most suited for treatment with ruxolitinib cream as monotherapy. In the second clinical expert's opinion, patients with AD could receive ruxolitinib cream treatment regardless of response to or eligibility for TCS and/or TCI treatments. As well, the second clinical expert felt that

patients with over 10% BSA affected might still be eligible for ruxolitinib cream provided that the cream is applied to no more than 10% to 20% BSA.

According to the clinical experts, there is no universal definition for adequate (or inadequate) response to TCS and TCI treatment. They noted that treatment response to TCS and TCI is typically determined by clinical judgement on a case-by-case basis and patient satisfaction, although it might be reasonable to consider initiation of ruxolitinib cream treatment in patients whose skin fails to improve after 4 to 8 weeks of conventional topical therapy, including low-, mid-, or high- potency TCS, TCI, or crisaborole, as suggested in the sponsor's submission. From a clinical perspective, the clinical experts noted that ruxolitinib cream could also be considered prior to failure of existing topical treatments. The clinical experts noted that response to ruxolitinib cream treatment should similarly be assessed based on clinical judgement. They noted that EASI 75, which is the benchmark currently applied to renewal of systemic AD treatments reimbursement may not be applicable to ruxolitinib cream. The clinical experts explained that given that ruxolitinib cream may be used in combination with other topical treatments (applied to different affected areas), it is impossible to attribute changes in EASI score to ruxolitinib cream treatment in these scenarios. It is reasonable to conduct follow-up assessment at 8 weeks following treatment initiation, although a longer interval at 3 to 6 months may be more practical for patients with less severe disease, according to the clinical experts. Additionally, the clinical experts noted that given Canada's medical resource constraints, particularly access to dermatology visits but also to family physician and other physician visits, shorter follow-up intervals may be impractical. The clinical experts noted that treatment discontinuation could be considered in patients who have an inadequate response or intolerable AEs to ruxolitinib cream treatment. The clinical experts noted that ruxolitinib cream could be prescribed by any healthcare provider with experience in diagnosing, treating, and monitoring patients with AD; this would include principally general dermatologists, pediatricians, pediatric dermatologists, allergists, family practitioners, and nurse practitioners.

Clinician Group Input

The Canadian Dermatology Association, represented by 3 clinicians, and the Atlantic Dermatology Specialist Group, represented by 11 clinicians, submitted 2 separate inputs. Consistent with the input from the clinical experts consulted by CDA-AMC, the clinician groups indicated that some patients receiving existing treatments experience uncontrolled disease, side effects, poor tolerability with ointment formulation, or poor treatment adherence due to the need to apply different topical products to different body locations. They agreed that there is an unmet need for a new topical therapy that is effective, better tolerated, and in cream formulation. The clinician groups also noted that an effective topical therapy is needed to prevent the need to escalate to phototherapy or systemic treatments, which are associated with limitations (e.g., limited efficacy, accessibility, and drug coverage, side effects, monitoring required, high treatment cost). Both clinician groups also agreed that the main treatment goals include reduction in itch and inflammation (short- and long-term), achievement of skin clearance, minimizing tolerability and safety issues, improving quality of life, e.g., sleep, anxiety and depression. The clinical groups and clinical experts agreed that an ideal topical treatment should be in a cosmetically appropriate base, convenient to use, and accessible.

In general, 2 clinician groups and the clinical experts consulted by CDA-AMC agreed that ruxolitinib cream could be used in patients with AD who are not adequately controlled with topical prescription therapies (TCS, TCI), or when those therapies are not advisable. However, the Atlantic Dermatology Specialist Group and the clinical experts noted that there is potential for the ruxolitinib treatment to be used as a first-line agent in some patients. The clinician groups noted that eligible patients include those with mild-to-moderate AD with up to 20% BSA, severe localized AD, moderate-to-severe AD (EASI score greater than 16 and at least 10% BSA), and those who cannot access or have contraindications to phototherapy or systemic therapies. Consistent with the input form the clinical experts consulted by CDA-AMC, the clinician groups noted that ruxolitinib cream could be used as either monotherapy or adjunct (to systemic therapy if eligible and tolerated) for continuous or as-needed use. While the clinician groups felt that ruxolitinib cream could be used on any body sites in patients with up to 20% BSA affected, one of the clinical experts consulted by CDA-AMC felt that use of ruxolitinib cream should be mainly limited to face and intertriginous involvements only and applied to no more than 10% BSA due to potential systemic absorption and high treatment cost.

Both clinician groups and the clinical experts noted that the treatment response is typically assessed by signs and symptoms (e.g., itch and inflammation), BSA, extent of involvement of special sites (hands, feet, face, skin folds, or perineal area), and patient-reported outcomes, (e.g., health-related quality of life, functional impact). The clinician groups and one of the clinical experts consulted by CDA-AMC agreed that after a trial period of 8 weeks, if there is an inadequate improvement in signs and symptoms of disease, recurrent flares, worsening of disease, or intolerance/side effects, then discontinuation of the treatment would be

considered. The clinician groups' input also indicated that a 3 to 6 months follow up for response assessment in patients receiving topical treatments could be more favorable in the clinical practice, except in patients with more severe disease for whom an 8-week assessment interval would be appropriate. The clinician groups agreed that generalist or primary care physicians as well as specialists, e.g., dermatologists, allergy and immunology specialists, and pediatricians, who are comfortable with diagnosis and management of AD should prescribe, treat, and monitor patients who receive ruxolitinib cream.

Drug Program Input

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

- considerations for initiation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues

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

Clinical Evidence

Systematic Review

Description of Studies

The sponsor-conducted systematic literature review identified 2 identically-designed, pivotal, phase III, double-masked, randomized-controlled trials (RCTs; TRuE-AD1, N = 631; TRuE-AD2, N = 618) aiming to assess the efficacy and safety of ruxolitinib cream relative to vehicle cream, as monotherapy, in adolescents and adults aged 12 years or above with AD of mild (Investigator's Global Assessment [IGA] score of 2) or moderate (IGA score of 3) severity, and 3% to 20% of BSA affected by AD. Patients were randomized to receive ruxolitinib 1.5% cream, ruxolitinib 0.75% cream, or vehicle cream monotherapy in a 2:2:1 ratio for a 8-week vehicle-controlled (VC) period, followed by a 44-week long-term safety (LTS) period. In the LTS period, patients who initially received vehicle cream in the VC period were re-randomized to 1 of the 2 ruxolitinib cream treatment groups to receive treatment on an as-needed basis, while patients who initially received ruxolitinib cream continued to receive the same intervention as-needed. In both trials, the primary end point was the proportion of patients achieving Investigator's Global Assessment-Treatment Success (IGA-TS, i.e., IGA score of 0 or 1 with at least 2 grade improvement from baseline) at week 8, and the key secondary end points were proportion of patients achieving EASI-75 (i.e., at least 75% improvement [i.e., reduction] from baseline in EASI score), at least 4-point improvement (i.e., reduction) from baseline in Itch numeric rating scale (NRS) score, at least 6-point improvement (i.e., reduction) from baseline in Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form – Sleep Disturbance (8b – 24-hour recall) score, and at least 6-point improvement (i.e., reduction) from baseline in PROMIS Short Form – Sleep-related Impairment (8a – 24-hour recall) score, at week 8.

At baseline, the majority of patients in both trials were adults (TRuE-AD1, 80.5%; TRuE-AD2, 80.3%) and had IGA score of 3 (TRuE-AD1, 75.9%; TRuE-AD2, 74.1%). The mean total percent BSA affected by AD was 9.5% in TRuE-AD1 and 10.0% in TRuE-AD2. Prior TCI treatment was noted in 24.1% and 18.8 % of patients in TRuE-AD1 and TRuE-AD2, respectively. Prior medium-, high-, super high-potency TCS treatment was noted in 43.7%, 34.9%, and 8.9% of patients, respectively, in TRuE-AD1; and in 41.1%, 30.4%, 7.0% of patients, respectively, in TRuE-AD2. The proportion of patients who had inadequate disease control with TCS and/or TCI, or whom such treatments are not advisable, was not reported. A small proportion of patients received prior systemic immunosuppressants, phototherapy, dupilumab, and systemic Janus kinase (JAK) inhibitor treatment.

Efficacy Results

Note that efficacy and safety results of ruxolitinib 0.75% cream group are not presented in this report since this strength of ruxolitinib cream is not approved by Health Canada for the treatment of AD and is not of interest to this review. In addition, the study inclusion and exclusion criteria did not restrict entry based on prior experience with topical treatments, and the sponsor was unable to provide subgroup data in the patient population as per the Health Canada indication (patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable) upon the review team's request. However, the sponsor provided post-hoc analyses using the pooled data from both trials by topical treatment history (TCS only, TCI only, TCS plus TCI – regardless of treatment timeframe and in patients who received topical treatment within 30 days prior to screening) as supportive evidence for select outcomes. Results of the full study population, along with the post-hoc subgroup analyses, are presented in the following text.

IGA score

IGA-TS

The proportion of patients achieving IGA-TS at week 8 was the primary endpoint in both trials. At week 8, the between-group difference comparing ruxolitinib 1.5% cream with vehicle cream was 38.7% (95% confidence interval [CI], 29.9% to 47.4%; P<0.0001) in the TRuE-AD1 trial and 43.7% (CI, 35.6% to 51.8%; P<0.0001) in the TRuE-AD2 trial, both of which were in favour of ruxolitinib 1.5% cream. Results of the pre-specified exploratory subgroup and sensitivity analyses were consistent in direction with the primary analysis in both trials. Subgroup analyses in both trials seem to suggest a higher IGA-TS response rate at week 8 in patients with baseline IGA score of 3 (versus IGA score of 2), EASI score greater than 7 (versus EASI score 7 or less), and patients in Europe (versus in North America).

A post-hoc subgroup analysis by topical treatment history showed results consistent with the primary analysis across subgroups (TCS only, TCI only, TCS plus TCI – regardless of treatment timeframe and in patients who received topical treatment within 30 days prior to screening).

IGA-TS was not assessed at week 52 in both trials.

IGA 0/1

The proportion of patients achieving an IGA score of 0 or 1 was a secondary endpoint at week 52 in both trials. At week 52, the proportions of patients achieving an IGA score of 0 or 1 in the vehicle cream to ruxolitinib 1.5% cream group and the ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group were 73.7% and 75.4%, respectively, in the TRuE-AD1 trial; and 74.4% and 80.1%, respectively, in the TRuE-AD2 trial.

In a post-hoc subgroup analysis by topical treatment history, the vehicle cream to ruxolitinib 1.5% cream group achieved a similar IGA 0/1 response rate at week 52 as the ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group across patients who received TCS only, TCI only, and TCS and TCI – regardless of treatment timeframe and in patients who received topical treatment within 30 days prior to screening.

EASI score

EASI-75

The proportion of patients achieving EASI-75 at week 8 was a key secondary endpoint and was adjusted for multiplicity in both trials. At week 8, the between-group difference comparing ruxolitinib 1.5% cream with vehicle cream was 37.5% (95% CI, 27.8% to 47.1%; P<0.0001) in the TRuE-AD1 trial and 47.4% (95% CI, 38.5% to 56.4%; P<0.0001) in the TRuE-AD2 trial, both of which were in favour of ruxolitinib 1.5% cream. In both trials, results of the sensitivity analyses were consistent with the primary analysis. Results of the pre-specified subgroup analyses showed a consistent direction of effect as the primary analysis. Subgroup analyses in both trials seem to suggest a higher EASI-75 response rate at week 8 in patients with baseline EASI score greater than 7 (versus EASI score 7 or less).

A post-hoc subgroup analysis by topical treatment history showed results consistent in direction with the primary analysis across subgroups, as (TCS only, TCI only, TCS plus TCI – regardless of treatment timeframe and in patients who received topical treatment within 30 days prior to screening).

EASI-75 was not assessed at week 52 in both trials.

AD Afflicted %BSA

Change from baseline in AD afflicted percent BSA at weeks 8 and 12 were secondary endpoints and were not adjusted for multiplicity in both trials. At week 8, the between-group least-square mean (LSM) difference comparing ruxolitinib 1.5% cream with vehicle cream was -3.7% (95% CI, -4.7% to -2.8%) in the TRuE-AD1 trial and -4.5% (95% CI, -5.5% to -3.6%) in the TRuE-AD2 trial.

In both trials, reduction in AD afflicted percent BSA was sustained at week 52 in patients who continued to receive ruxolitinib 1.5% cream in the LTS period (ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group). The vehicle cream to ruxolitinib 1.5% cream group achieved AD afflicted percent BSA similar to that of the ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group at week 52 in both trials. In a post-hoc subgroup analysis by topical treatment history, the vehicle cream to ruxolitinib 1.5% cream group achieved a similar total percent BSA afflicted by AD at week 52 as the ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group across patients who received TCS only, TCI only, and TCS and TCI (regardless of treatment timeframe and in patients whom topical treatment was received within 30 days prior to screening).

Itch NRS score

≥4 improvement in Itch NRS from baseline

The proportion of patients with at least 4 points of improvement in Itch NRS from baseline (among patients with a baseline score of at least 4; vehicle: n = 78 in TRuE-AD1, n = 80 in TRuE-AD2; ruxolitinib: n = 161 in TRuE-AD1, n = 146 in TRuE-AD2) at week 8 was a key secondary endpoint and was adjusted for multiplicity in both trials. At week 8, the between-group difference comparing ruxolitinib 1.5% cream with vehicle cream was 36.8% (95% CI, 25.7% to 47.9%; P<0.0001) in the TRuE-AD1 trial and 34.4% (95% CI, 23.0% to 45.9%; P<0.0001) in the TRuE-AD2 trial, both of which were in favour of ruxolitinib 1.5% cream. A post-hoc subgroup analysis by topical treatment history showed results consistent in direction with the primary analysis across subgroups (TCS only, TCI only, TCS plus TCI – regardless of treatment timeframe and in patients who received topical treatment within 30 days prior to screening).

This endpoint was not assessed at week 52 in both trials.

Patient Oriented Eczema Measure (POEM)

Change from baseline in POEM

Change from baseline in POEM score at weeks 8 and 52 were secondary endpoints and were not adjusted for multiplicity in both trials. At week 8, the between-group LSM difference comparing ruxolitinib 1.5% cream with vehicle cream was -6.3 (95% CI, -7.6 to -5.0) in the TRuE-AD1 trial and -5.9 (95% CI, -7.2 to -4.7) in the TRuE-AD2 trial.

In both trials, reduction in POEM score was sustained at week 52 in patients who continued to receive ruxolitinib 1.5% cream in the LTS period (ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group). The vehicle cream to ruxolitinib 1.5% cream group achieved a mean POEM score similar to that of the ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group at week 52 in both trials.

PROMIS Short Form – Sleep Disturbance

≥ 6-point improvement (24-hour recall)

The proportion of patients with at least a 6-point improvement in PROMIS Short Form – Sleep Disturbance score (24-hour recall) from baseline (among patients with a baseline score of at least 6; vehicle: n = 116 in TRuE-AD1, n = 110 in TRuE-AD2; ruxolitinib: n = 238 in TRuE-AD1, n = 211 in TRuE-AD2) at week 8 was a key secondary endpoint and was adjusted for multiplicity in both trials. The between-group difference comparing ruxolitinib 1.5% cream with vehicle cream was 12.8% (95% CI, 5.3% to 20.3%; P = 0.0039) in the TRuE-AD1 trial, in favour of ruxolitinib 1.5% cream. In the TRuE-AD2 trial, the between-group difference was 6.5%

(95% CI, -2.9% to 15.9%; P = 0.2359) trial, which did not favour either study intervention; no superiority testing was conducted for the efficacy endpoint lower in the statistical testing hierarchy (i.e., proportion of patients with at least 6 points of improvement in in PROMIS Short Form- Sleep-related Impairment score at week 8). This endpoint was not assessed at week 52 in both trials.

PROMIS Short Form – Sleep-related Impairment

≥6-point improvement (24-hour recall)

The proportion of patients with a 6-points improvement in PROMIS Short Form – Sleep Impairment score (24-hour recall) from baseline (among patients with a baseline score of at least 6; vehicle: n = 114 in TRuE-AD1, n = 111 in TRuE-AD2; ruxolitinib: n = 245 in TRuE-AD1, n = 212 in TRuE-AD2) at week 8 was a key secondary endpoint in both trials. This endpoint was included in the statistical testing hierarchy, but no superiority testing was conducted due to prior failure in the hierarchy. At week 8, the between-group difference comparing ruxolitinib 1.5% cream with vehicle cream was 8.4% (95% CI, 0.4% to 16.4%) in the TRuE-AD1 trial and 9.6% (95% CI, 1.4% to 18.4%) in the TRuE-AD2 trial. This endpoint was not assessed at week 52 in both trials.

Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI) scores

Change from baseline in DLQI

Change in DLQI score from baseline (among patients 16 years of age or older; vehicle: n = 82 in TRuE-AD1, n = 87 in TRuE-AD2; ruxolitinib: n = 201 in TRuE-AD1, n = 185 in TRuE-AD2) at weeks 8 and 52 were secondary endpoints and were not adjusted for multiplicity in both trials. At week 8, the between-group least-square mean (LSM) difference comparing ruxolitinib 1.5% cream with vehicle cream was -4.5 (95% CI, -5.6 to -3.4) in the TRuE-AD1 trial and -2.8 (95% CI, -3.7 to -1.8) in the TRuE-AD2 trial. Results of the responder analysis (proportion of patients achieving at least 4-point improvement in DLQI score) at week 8 were similarly in favour of ruxolitinib cream in both trials [redacted].

In both trials, improvement (i.e., reduction) from baseline in DLQI score was sustained at week 52 in patients who continued to receive ruxolitinib 1.5% cream in the LTS period (ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group). The vehicle cream to ruxolitinib 1.5% cream group achieved a mean DLQI score similar to that of the ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group at week 52 in both trials.

Change from baseline in CDLQI

Change in CDLQI score from baseline (among patients less than 16 years of age; vehicle: n = 16 in TRuE-AD1, n = 11 in TRuE-AD2; ruxolitinib: n = 28 in TRuE-AD1, n = 25 in TRuE-AD2) at weeks 8 and 52 were secondary endpoints and were not adjusted for multiplicity in both trials. At week 8, the between-group LSM difference comparing ruxolitinib 1.5% cream with vehicle cream was -2.3 (95% CI, -4.4 to -0.1 points) in the TRuE-AD1 trial and -3.1 points (95% CI, -6.3 to 0.1 points) in the TRuE-AD2 trial.

In both trials, improvement (i.e., reduction) from baseline in CDLQI score was sustained at week 52 in patients who continued to receive ruxolitinib 1.5% cream in the LTS period (ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group). The vehicle cream to ruxolitinib 1.5% cream group achieved a mean CDLQI score similar to that of the ruxolitinib 1.5% cream to ruxolitinib 1.5% cream group at week 52 in both trials.

Harms Results

Adverse Events

In the VC period, the proportion of patients who reported at least 1 TEAE was lower in the ruxolitinib 1.5% cream group compared with the vehicle cream group in both trials (TRuE-AD1, 29.2% vs 34.9%; TRuEAD-2, 23.6% vs 31.5%). The difference appears to be partly attributable to including AD as a harm. In the LTS period, the proportion of patients who reported at least 1 TEAEs was higher in the ruxolitinib 1.5% cream group (53.5%) compared with the vehicle cream group (48.9%) in the TRuE-AD1 trial, but lower compared with the vehicle cream group in the TRuE-AD2 trial (ruxolitinib, 54.3%; vehicle, 65.4%).

The most common TEAEs of ruxolitinib 1.5% cream were upper respiratory tract infection, nasopharyngitis, and headache in the VC and LTS periods.

Serious Adverse Events

In the VC period, serious TEAEs were reported in 2 (1.6%) patients in the vehicle cream group and 2 (0.8%) patients in the ruxolitinib 1.5% cream group in the TRuE-AD1 trial. In the TRuE-AD2 trial, no patient reported serious TEAE in the vehicle cream group and 1 (0.4%) patient reported serious TEAE in the ruxolitinib 1.5% cream group. A similarly low frequency of serious TEAEs were noted in both treatment arms of the trials in the LTS period.

Withdrawals Due to Adverse Events

In the VC period, study treatment withdrawal due to TEAE was reported in 5 (4.0%) patients in the vehicle cream group and 3 (1.2%) patients in the ruxolitinib 1.5% cream group in the TRuE-AD1 trial; in 3 (2.4%) patients in the vehicle cream group and 1 (0.4%) patient in the ruxolitinib 1.5% cream group in the TRuE-AD2 trial. TEAE leading discontinuing ruxolitinib cream treatment included papule, generalized pruritus, urticaria (1 [0.4%] patient each in TRuE-AD1) and cerebrovascular accident (1 [0.4%] patient in TRuE-AD2). In the LTS period of both studies, no patient withdrew from study treatment due to TEAE.

Mortality

No death was reported during the VC and LTS periods in both trials.

Critical Appraisal

The trials used adequate methods of randomization and allocation concealment. There were few small baseline imbalances in patient characteristics that may be compatible with chance and were not believed to substantially impact study results. The trials were adequately masked to reduce bias; however, there is a small potential for bias in measurement of patient-reported outcomes (i.e., itch NRS, POEM, PROMIS short form-sleep disturbance, PROMIS short form-sleep related impairment, DLQI, and CDLQI scores) leading to inflated efficacy of ruxolitinib cream due to possible un-masking in patients becoming aware of their assignments based on treatment response. Responder analyses of IGA-TS, EASI-75, itch NRS, and PROMIS short -sleep disturbance and sleep-related impairment scores at week 8 were controlled for multiplicity, while other outcomes (IGA 0 or 1, change from baseline in percent BSA afflicted by AD, POEM, DLQI and CDLQI scores) were not and were at an increased risk of type 1 error (false positive results). At least 30% of patients were excluded from each treatment group in the itch NRS responder analysis (due to baseline itch NRS score being less than 4 points), which could potentially impact randomization, although the extent and direction of the resulting bias is unclear. There is a risk of potential attrition bias in favour of ruxolitinib cream with respect to continuous secondary endpoints in the VC period given that study treatment discontinuation in the vehicle cream group was notably higher compared with the ruxolitinib cream group. Implicit imputation using mixed model for repeated measures (MMRM) under the missing-at-random assumption (MAR) was applied to account for missing data, although it is unclear if the MAR assumption holds when the reasons for patient withdrawal (most common reason for discontinuation) were not documented; as well, no sensitivity analysis was conducted. The endpoint of change from baseline in CDLQI scores was based on a small size in both treatment groups, which could lead to instability of the treatment effect estimates. There is a lack of sample size consideration and control for multiplicity for subgroup analyses, which preclude definitive conclusions on subgroup effects. No firm conclusion can be drawn on results of the LTS period due to the absence of a control group, potential selection bias, and sizable loss to follow-up (approximately 20%) in both trials.

The sponsor's funding request (aligned with the Health Canada indication) was for the topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies (TCS, TCI) or when those therapies are not advisable. However, the inclusion and exclusion criteria of the pivotal trials did not restrict entry based on prior experience with TCS and TCI treatment. Post-hoc subgroup analyses in patients with recent history of TCS and/or TCI treatment was submitted by the sponsor as supporting evidence. Nonetheless, in consultation with the clinical experts, the review team considered that it is unclear if this subgroup population could adequately reflect most patients expected to receive ruxolitinib cream in clinical practice (i.e., patients with AD who are inadequately controlled with TCS and/or TCI treatment, or whom these treatments are inadvisable). The clinical experts considered that the baseline patient characteristics in the pivotal studies were in general reflective of the patient population eligible for ruxolitinib cream in clinical practice, although the proportion of patients with mild disease (IGA score of 2), previous TCI treatment, and previous TCS treatment of medium, high, or super high potency in the trials appear to be lower than expected in clinical practice. As per clinical expert input, the duration of safety follow-up of 52 weeks was inadequate for capturing the long-term safety of ruxolitinib cream (including rare

harms) given that AD is a lifelong condition requiring treatment over many years. The absence of head-to-head evidence comparing ruxolitinib cream with relevant comparators (systemic immunosuppressants, biologics, and JAK inhibitors) in patients with moderate AD, and evidence for ruxolitinib cream in combination with other topical therapies represents gaps in evidence in the treatment of AD. Generalizability of study results to the adolescent patient population in clinical practice could potentially be limited by the small proportion of adolescents enrolled in the trials (approximately 20%). Of note, a similarly small proportion of adolescent patients was observed in other clinical trials for AD treatments.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CDA-AMC's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working. Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- Severity and extent of AD (proportion of patients achieving IGA-TS, IGA 0/1, and EASI-75; change in percent BSA afflicted by AD from baseline
- Symptom control (proportion of patients achieving at least 4-point improvement in itch NRS score from baseline, at least 6-point improvement in in PROMIS Short Form – Sleep Disturbance score from baseline, at least 6-point improvement in in PROMIS Short Form – Sleep-related Impairment score from baseline; change in POEM score from baseline)
- Health-related quality of life (HRQoL; change in DLQI and CDLQI scores from baseline)
- Harms (serious adverse events [SAEs])

The GRADE summary of findings for ruxolitinib 1.5% cream versus vehicle for the treatment of patients with AD is presented in Table 1.

Table 1: Summary of Findings for Ruxolitinib 1.5% cream Versus Vehicle for Patients With Mild to Moderate Atopic Dermatitis whose Disease is not Adequately Controlled with Topical Therapies or when those Therapies are not Advisable

Outcome and follow-up	Patients (studies), N	Absolute effect	Certainty	What happens
Extent and severity of disease				
IGA-TS (i.e., IGA score 0 [clear] or 1 [almost clear] with ≥ 2-point reduction from baseline), proportion of patients achieving IGA-TS (95% CI) Follow-up: 8 weeks	725 (2 RCTs)	TRuE-AD1 • Ruxolitinib: 538 per 1,000 (NR) • Vehicle: 151 per 1,000 (NR) • Difference: 387 more per 1,000 (299 more to 474 more per 1,000) TRuE-AD2 • Ruxolitinib: 513 per 1,000 (NR) • Vehicle: 76 per 1,000 (NR) • Difference: 437 more (356 more to 518 more per 1,000)	Moderate[a,b]	Ruxolitinib 1.5% cream likely results in a clinically important increase in IGA-TS response when compared with placebo.
IGA score (5-point scale, 0 [clear] to 4 [severe]), proportion of patients achieving IGA score of 0 (clear) or 1 (almost clear) (95% CI) Follow-up: 52 weeks	423 (non-comparative from 2 RCTs)	TRuE-AD1 • Ruxolitinib: 754 per 1,000 (NR) • Vehicle to ruxolitinib: 737 per 1,000 (NR) • Difference: NA TRuE-AD2 • Ruxolitinib: 801 per 1,000 (NR) • Vehicle to ruxolitinib: 744 per 1,000 (NR) • Difference: NA	Very low[c]	The evidence is very uncertain about the effect of ruxolitinib 1.5% cream on achieving IGA score of 0 or 1 when compared with any comparator.
EASI score (0 [clear] to 72 [very severe]), proportion of patients achieving EASI-75 (i.e., at least 75% reduction in score from baseline) (95% CI) Follow-up: 8 weeks	725 (2 RCTs)	TRuE-AD1 • Ruxolitinib: 621 per 1,000 (NR) • Vehicle: 246 per 1,000 (NR) • Difference: 375 more per 1,000 (278 more to 471 more per 1,000) TRuE-AD2 • Ruxolitinib: 618 per 1,000 (NR) • Vehicle: 144 per 1,000 (NR) • Difference: 474 more (385 more to 564 more per 1,000)	Moderate[a,b]	Ruxolitinib 1.5% cream likely results in a clinically important increase in EASI-75 response when compared with placebo.
LSM change from baseline in AD afflicted %BSA, % (95% CI) Follow-up: 8 weeks	652 (2 RCTs)	TRuE-AD1 • Ruxolitinib: -6.7% (NR) • Vehicle: -3.0% (NR) • Difference: -3.7% (-4.7% to -2.8%)[f] TRuE-AD2 • Ruxolitinib: -6.7% (NR) • Vehicle: -2.2% (NR) • Difference: -4.5% (-5.5% to -3.6%)[f]	Low[b,d,e]	Ruxolitinib 1.5% cream may result in little to no clinically important difference in percent BSA afflicted by AD when compared with placebo.

Outcome and follow-up	Patients (studies), N	Absolute effect	Certainty	What happens
Change from baseline in AD afflicted %BSA, % (95% CI) Follow-up: 52 weeks	424 (non-comparative from 2 RCTs)	TRuE-AD1 • Ruxolitinib: -8.1% (NR) • Vehicle to ruxolitinib: -4.9% (NR) • Difference: NA TRuE-AD2 • Ruxolitinib: -8.4% (NR) • Vehicle to ruxolitinib: -6.8% (NR) • Difference: NA	Very low[c]	The evidence is very uncertain about the effect of ruxolitinib 1.5% cream on percent BSA afflicted by AD when compared with any comparator.
Symptom control				
Itch NRS score (0 [no itch] to 10 [worst imaginable itch]), proportion of patients with ≥4 point improvement from baseline (95% CI) Follow-up: 8 weeks	465 (2 RCTs)	TRuE-AD1 • Ruxolitinib: 522 per 1,000 (NR) • Vehicle: 154 per 1,000 (NR) • Difference: 368 more per 1,000 (257 more to 479 more per 1,000) TRuE-AD2 • Ruxolitinib: 507 per 1,000 (NR) • Vehicle: 163 per 1,000 (NR) • Difference: 344 more per 1,000 (230 more to 459 more per 1,000)	Low[b,g]	Ruxolitinib 1.5% cream may result in a clinically important increase in the proportion of patients with ≥ 4 point improvement in itch NRS score when compared with placebo.
POEM score (0 [clear] to 28 [very severe]), LSM change from baseline in score (95% CI) Follow-up: 8 weeks	635 (2 RCTs)	TRuE-AD1 • Ruxolitinib: -11.5 (NR) • Vehicle: -5.2 (NR) • Difference: -6.3 (-7.6 to -5.0)[f] TRuE-AD2 • Ruxolitinib: -10.0 (NR) • Vehicle: -4.0% (NR) • Difference: -5.9 (-7.2 to -4.7)[f]	Low[b,d,h]	Ruxolitinib 1.5% cream may result in a clinically important improvement in POEM score when compared with placebo.
POEM score (0 [clear] to 28 [very severe]), change from baseline in score (95% CI) Follow-up: 52 weeks	412 (non-comparative from 2 RCTs)	TRuE-AD1 • Ruxolitinib: -10.6 (NR) • Vehicle to ruxolitinib: -7.0 (NR) • Difference: NA TRuE-AD2 • Ruxolitinib: -10.7 (NR) • Vehicle to ruxolitinib: -6.3 (NR) • Difference: NA	Very low[c]	The evidence is very uncertain about the effect of ruxolitinib 1.5% cream on POEM score when compared with any comparator.
PROMIS Short Form – sleep disturbance score (8 [no disturbance] and 40 [severe disturbance], proportion of patients with ≥ 6-point	675 (2 RCTs)	TRuE-AD1 • Ruxolitinib: 223 per 1,000 (NR) • Vehicle: 95 per 1,000 (NR) • Difference: 128 more per 1,000 (53 more to 203 more per 1,000) TRuE-AD2	Low[a,b,i]	Ruxolitinib 1.5% cream may result in a clinically important increase in proportion of patients with ≥ 6-point improvement in PROMIS Short

Outcome and follow-up	Patients (studies), N	Absolute effect	Certainty	What happens
improvement (24-hour recall) from baseline (95% CI) Follow-up: 8 weeks		• Ruxolitinib: 256 per 1,000 (NR) • Vehicle: 191 per 1,000 (NR) • Difference: 65 more per 1,000 (29 less to 159 more per 1,000)		Form – sleep disturbance score when compared with placebo.
PROMIS Short Form – sleep-related impairment score (8 [no impairment] and 40 [severe impairment], proportion of patients with ≥ 6-point improvement (24-hour recall) from baseline (95% CI) Follow-up: 8 weeks	682 (2 RCTs)	TRuE-AD1 • Ruxolitinib: 216 per 1,000 (NR) • Vehicle: 132 per 1,000 (NR) • Difference: 84 more per 1,000 (4 more to 164 more per 1,000)[j] TRuE-AD2 • Ruxolitinib: 231 per 1,000 (NR) • Vehicle: 135 per 1,000 (NR) • Difference: 96 more per 1,000 (14 more to 184 more per 1,000)[j]	Low[a,b,k]	Ruxolitinib 1.5% cream may result in a clinically important increase in proportion of patients with ≥ 6-point improvement in PROMIS Short Form – sleep disturbance score when compared with placebo.
HRQoL				
DLQI score (0 [best] to 30 [worst]), LSM change from baseline in score (95% CI) Follow-up: 8 weeks	555 (2 RCTs)	TRuE-AD1 • Ruxolitinib: -7.5 (NR) • Vehicle: -3.1 (NR) • Difference: -4.5 (-5.6 to -3.4)[f] TRuE-AD2 • Ruxolitinib: -6.3 (NR) • Vehicle: -3.5 (NR) • Difference: -2.8 (-3.7 to -1.8)[f]	Low[b,d,l]	Ruxolitinib 1.5% cream may result in a clinically important improvement in DLQI score when compared with placebo.
DLQI score (0 [best] to 30 [worst]), change from baseline in score (95% CI) Follow-up: 52 weeks	362 (non-comparative from 2 RCTs)	TRuE-AD1 • Ruxolitinib: -7.7 (NR) • Vehicle to ruxolitinib: -4.8 (NR) • Difference: NA TRuE-AD2 • Ruxolitinib: -7.3 (NR) • Vehicle to ruxolitinib: -3.2 (NR) • Difference: NA	Very low[c]	The evidence is very uncertain about the effect of ruxolitinib 1.5% cream on DLQI score when compared with any comparator.
CDLQI score (0 [best] to 30 [worst]), LSM change from baseline in score (95% CI) Follow-up: 8 weeks	80 (2 RCTs)	TRuE-AD1 • Ruxolitinib: -6.1 (NR) • Vehicle: -3.8 (NR) • Difference: -2.3 (-4.4 to -0.1)[f] TRuE-AD2 • Ruxolitinib: -4.4 (NR) • Vehicle: -1.3 (NR) • Difference: -3.1 (-6.3 to 0.1)[f]	Low[b,m]	Ruxolitinib 1.5% cream may result little to no clinically important improvement in CDLQI score when compared with placebo.

Outcome and follow-up	Patients (studies), N	Absolute effect	Certainty	What happens
CDLQI score (0 [best] to 30 [worst]), change from baseline in score (95% CI) Follow-up: 52 weeks	50 (non-comparative from 2 RCTs)	TRuE-AD1 • Ruxolitinib: -9.7 (NR) • Vehicle to ruxolitinib: -0.4 (NR) • Difference: NA TRuE-AD2 • Ruxolitinib: -6.6 (NR) • Vehicle to ruxolitinib: -6.4 (NR) • Difference: NA	Very low[c]	The evidence is very uncertain about the effect of ruxolitinib 1.5% cream on CDLQI score when compared with any comparator.
Harms				
Serious adverse events Follow-up: 8 weeks	749 (2 RCTs)	TRuE-AD1 • Ruxolitinib: 8 per 1,000 (NR) • Vehicle: 16 per 1,000 (NR) • Difference: NR TRuE-AD2 • Ruxolitinib: 4 per 1,000 (NR) • Vehicle: 0 per 1,000 (NR) • Difference: NR	Moderate[n]	Ruxolitinib 1.5% cream likely result in little to no clinically important difference in serious adverse events when compared with placebo.
Serious adverse events Follow-up: 52 weeks	545 (non-comparative from 2 RCTs)	TRuE-AD1 • Ruxolitinib: 13 per 1,000 (NR) • Vehicle to ruxolitinib: 21 per 1,000 (NR) • Difference: NA TRuE-AD2 • Ruxolitinib: 14 per 1,000 (NR) • Vehicle to ruxolitinib: 0 per 1,000 (NR) • Difference: NA	Very low[c]	The evidence is very uncertain about the effect of ruxolitinib 1.5% cream on the frequency of serious adverse events when compared with any comparator.

AD = atopic dermatitis; BSA= body surface area; CI = confidence interval; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = eczema area and severity index; HRQoL = health-related quality of life; IGA = investigator global assessment; IGA-TS = investigator global assessment-treatment success; LSM = least square mean; NA = not applicable; NR = not reported; NRS = numeric rating scale; POEM = Patient Oriented Eczema Measure; PROMIS = Patient-reported Outcomes Measurement Information System; RCT = Randomized controlled trial.

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

[a] Did not rate down for study limitations. Notable imbalance in mean number of flares in the past 12 months at baseline between treatment groups in TRuE-AD1, which could potentially result in bias in favour of ruxolitinib cream as per clinical expert input. Such imbalance was not observed in the identically designed TRuE-AD2 study, which showed similar results as TRuE-AD1. Imbalance noted in TRuE-AD1 was compatible with chance.

[b] –1 level for serious indirectness. The clinical experts consulted for this review anticipated that in most patients, ruxolitinib cream would be used when AD is inadequately controlled with TCS and/or TCI treatment, or these treatments are inadvisable. It is unclear if the trial population was reflective of the patient population in clinical practice since the inclusion and exclusion criteria of the trial did not restrict entry based on prior experience with TCS and TCI treatment. Other considerations included the lower proportion of patients with mild disease (IGA score of 2) at baseline in trials versus clinical practice. Baseline IGA score is a potential treatment effect modifier, as per clinical expert input.

[c] In absence of a comparator arm, conclusions about efficacy relative to any comparator cannot be drawn and certainty of evidence started at very low without an opportunity to rate up.

[d] –1 level for serious study limitations. Study treatment discontinuation in the VC period was notably higher in the vehicle cream group compared to the ruxolitinib cream group in both trials which could potentially lead to attrition bias in favour of ruxolitinib cream. It is unclear if the imputation method used was appropriate to account for missing data. Did not rate down for imbalance in mean number of flares at baseline, which was considered by the review team to be compatible with chance.

[e] The clinical experts consulted for this review indicated that a 5% to 10% between-group difference could be considered clinically important. Based on the lower limit of the minimal important difference (MID) estimates (i.e., 5% difference), Did not rate down for imprecision; the 95% CI in TRuE-AD2 included the possibility of benefit and no difference, however, this was not considered to be a source of serious imprecision due to its proximity to -5%. Note that if the upper limit of the MID (i.e., 10 % difference) was used instead, the review team would not rate down imprecision given that both 95% CIs excluded the possibility of benefit. The overall rating of certainty would remain as low.

[f] Statistical testing for this outcome was not adjusted for multiplicity. The results are considered as supportive evidence.

[g] –1 level for serious study limitations. A large proportion of patients with baseline score of less than 4 (at least 30% in each treatment group) were excluded from the analysis, which could potentially impact randomization. The extent and direction of the resulting bias is however unclear.
[h] Literature-identified MID estimates ranged between 3.4 to 5 points. Did not rate down imprecision regardless of whether the lower or upper limit of MID estimates was used. Based on the lower limit of MID estimates (i.e., 3.4-point difference); both 95% CIs included the possibility of benefit. Based on the upper limit of MID estimates (i.e., 5-point difference), although the upper boundary of the 95% CI in TRuE-AD1 and TRuE-AD2 was -5.0 and -4.7, respectively, this was not considered to be a source of serious imprecision due to its proximity to -5.
[i] –1 level for serious imprecision. Based on clinical expert input, 50 more per 1,000 patients achieving ≥ 6-point improvement (24-hour recall) from baseline in PROMIS Short Form – Sleep Disturbance score could be considered clinically important. The 95% CI in TRuE-AD2 included the possibility of benefit and no difference.
[j] No formal statistical testing was conducted due to prior failure in the statistical testing hierarchy (PROMIS Short Form- Sleep Disturbance score). The findings can be considered supportive.
[k] –1 level for serious imprecision. Based on clinical expert input, 50 more per 1,000 patients achieving ≥ 6-point improvement (24-hour recall) from baseline in PROMIS Short Form – Sleep Impairment score could be considered clinically important. Both 95% CI included the possibility of benefit and no difference.
[l] Literature-identified MID estimates ranged between 3 to 5 points. The review team considered the treatment effect to be clinically important, given that the point estimates in both trials were above or in close proximity to the lower limit of the MID estimate (i.e., 3-point difference). The upper bound of the CI in TRuE-AD1 indicates no clinically important difference but the review team recognized that there is some uncertainty on whether the literature-identified MID could be reliably applied to the analysis of the between-group difference in change from baseline and thus, did not rate down on imprecision.
[m] –1 level for serious study limitations, there is a potential that the prognostic balance provided by the randomization is not fully preserved in this analysis since it was conducted in a small subset of patients, with no stratification involved. Literature-identified MID estimates ranged between 6 to 8 points. Based on the lower limit of MID estimates (i.e., 6-point difference), the review team did not rate down further for imprecision even though the lower boundary of the 95% CI was -6.3; this was not considered to be a source of serious imprecision due to its proximity to -6. Note that the rating on imprecision remains the same if the upper limit of MID estimates (i.e., 8-point difference) was used instead.
[n] – 1 level for serious indirectness. The duration of follow-up of 8 weeks is inadequate for capturing potential rare serious adverse events of ruxolitinib cream as per clinical expert input.

Source: Source: Clinical Study Reports for TRuE-AD1 and TRuE-AD2. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

Both the TRuE-AD1 and TRuE-AD2 trials had a 44-week extension phase assessing the efficacy and safety of ruxolitinib cream in patients who completed the 8-week VC period. Evidence from the extension phase was submitted as part of the pivotal trials and was summarized in the Systematic Review section.

Indirect Comparisons

Description of Study

In the absence of head-to-head evidence comparing ruxolitinib cream to other relevant therapies used in the treatment of mild to moderate AD, the sponsor submitted 1 indirect treatment comparison (ITC) indirectly comparing the treatment effect of ruxolitinib 1.5% cream to dupilumab, abrocitinib, and upadacitinib in patients with moderate AD, defined by the sponsor as IGA score of 3, EASI score of 16 or higher, and percent affected BSA of 10% or higher, via a frequentist network meta-analysis (NMA). Study outcomes included proportion of patients achieving IGA-TS, EASI-75, and improvement in itch NRS score of at least 4. No information on comparative harms was submitted. A total of 8 studies were included in the NMA.

Efficacy Results

IGA-TS

There was insufficient evidence to show a difference comparing ruxolitinib cream versus upadacitinib 30 mg and 15 mg, and dupilumab 300 mg because the 95% CIs for odds ratio (OR) were wide (comparing ruxolitinib 1.5% cream versus upadacitinib 30 mg, OR = 2.10 [95% CI, 0.10 to 44.41]; versus upadacitinib 15 mg, OR = 3.60 [95% CI, 0.17 to 76.04]; versus dupilumab 300 mg, OR = 6.69 [95% CI, 0.32 to 140.26]. Comparisons with abrocitinib 200 mg and 100 mg were not present in the evidence network for IGA-TS.

EASI-75

There was insufficient evidence to show a difference comparing ruxolitinib cream versus upadacitinib 30 mg and 15 mg, dupilumab 300 mg, and abrocitinib 200 mg and 100 mg because the 95% CIs for OR were wide (comparing ruxolitinib 1.5% cream versus upadacitinib 30 mg, OR = 1.56 [95% CI, 0.22 to 11.03]; versus upadacitinib 15 mg, OR = 2.56 [95% CI, 0.36 to 18.12]; versus dupilumab 300 mg, OR = 3.36 [95% CI, 0.47 to 23.87]; versus abrocitinib 200 mg, OR = 1.52 [95% CI, 0.17 to 13.39]; versus abrocitinib 100 mg OR = 3.10 [95% CI, 0.35 to 27.32]).

Itch NRS-4

There was insufficient evidence to show a difference comparing ruxolitinib cream versus upadacitinib 30 mg and 15 mg, and dupilumab 300 mg because the 95% CIs for OR were wide (upadacitinib 30 mg versus ruxolitinib 1.5% cream, OR = 2.42 [95% CI, 0.46 to 12.79]; upadacitinib 15 mg versus ruxolitinib 1.5% cream, OR = 1.65 [95% CI, 0.31 to 8.74]; dupilumab 300 mg versus ruxolitinib 1.5% cream, OR = 1.19 [95% CI, 0.22 to 6.32]). Comparisons with abrocitinib 200 mg and 100 mg were not present in the evidence network for itch NRS-4.

Harms Results

Harms outcomes were not assessed.

Critical Appraisal

The validity of the results of the NMA was uncertain because the key assumptions of the analysis, homogeneity and consistency, could not be determined due to insufficient reporting of baseline patient characteristics in the moderate-only subgroup and a sparse network without a closed loop connecting ruxolitinib cream. For trials where the information was available, there was evidence of heterogeneity in patient populations (i.e., age group, history of disease control with or, eligibility for, topical AD treatment) between studies. Only 4 of 12 included studies reported baseline patient characteristics of the moderate-only subgroup; heterogeneity in disease severity and duration of AD diagnosis were noted between these studies and were not accounted for. These limitations result in uncertainty in the relative treatment effect estimates between ruxolitinib cream and the comparators. It is worth noting that

there is a risk of missing results in the synthesis given that close to half of the studies initially identified by the SLR were excluded due to the absence of available results for subgroups consisting of solely of moderate severity. Lastly, the absence of comparative evidence between ruxolitinib cream monotherapy and systemic immunosuppressants in patients with moderate AD, and the absence of comparative evidence for ruxolitinib cream as a combination therapy (in combination with other topical treatments), represent gaps in evidence in the treatment of AD.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Studies

One Phase II, open-label study (SCRATCH-AD) at a single Canadian site has been provided as supportive evidence regarding short-term clinical benefits of ruxolitinib 1.5% cream in adults with AD to control itch and reduce severity. The maximum study duration per participant was approximately 80 days, including the run-in period in which participants had a baseline mean PP-NRS score $\geq$ 4.0 during Days -7 to -1. Other key inclusion criteria were BSA involvement of 1% to 20% and IGA $\geq$ 2 on Day 1. Key exclusion criteria were significant flares in the previous 4 weeks, known immune deficiency or immunocompromised condition, use of any systemic corticosteroids or phototherapy, JAK inhibitors within 4 weeks prior, and dupilumab use within 26 weeks prior to the run-in period. Patients received ruxolitinib 1.5% cream applied topically twice daily (morning and evening approximately 12 hours between applications) from Day 1 until the day prior to the Day 29 visit. The primary end point was change from baseline PP-NRS at Day 2 (24-hour recall period after the first application) and all data were analyzed descriptively. Concomitant use of emollient was permitted. No other concomitant AD treatments were permitted.

Of 84 individuals who were screened, 35 (41.7%) did not pass the screening. Forty-nine participants applied ruxolitinib 1.5% at least once (Safety population) and 46 patients completed the run-in period and met all entry criteria, had baseline and at least 1 post-baseline PP-NRS or mPP-NRS assessment (modified intention-to-treat population). In Safety population (n = 49), the average age of participants was 35.6 years (standard deviation [SD] = 14.77 years), and the majority of participants were female (71.4%) and white (85.7%). At baseline, mean total percent BSA affected was 10.11% (SD = 5.34) and mean baseline EASI score was 7.23 (SD = 3.21). A mean PP-NRS score was 6.83 (SD = 1.4) and the majority of participants (87.8%) had an IGA score of 3. During the study period, median cumulative dose was 110.30 g (range = 2.4 to 335.9, n = 48) and the majority of participants (73.5%) used emollients and protectives, other analgesics and antipyretics (36.7%), NSAIDs and anti-rheumatic products (28.6%), inhaled adrenergics (22.4%), and vitamins A and D, including combinations of the 2 (20.4%).

Efficacy Results

On Day 2, a mean 3.37-point (SD = 1.85 points) or 50.57% (95% CI = 58.75% to 42.39%) reduction from baseline in PP-NRS (worst itch in the previous 24 hours) score was noted in the mITT population. The mean daily PP-NRS score decreased by 4.78-points (SD not reported) by Day 7 with a continued decrease, i.e., 5.68-point reduction (SD not reported) by Day 29. In the mITT population, increasing proportions of participants achieved IGA-TS at Days 8, 15, and 29, i.e., 45.5% (95% CI = 30.4% to 61.2%), 71.1% (95% CI = 55.7% to 83.6%), and 77.3% (95% CI = 62.2% to 88.5%), respectively. The mean change from baseline in IGA score at Days 8, 15, and 29 were -1.4 (SD = 0.73), -2.0 (SD = 0.87), and -2.2 (SD = 0.90), respectively.

Harms Results

Approximately one-third of participants (n = 15, 30.6%) had at least 1 treatment-emergent adverse event (TEAE). The most frequently reported TEAEs were COVID-19 (6.1%), and back pain, nasopharyngitis, headache, and upper respiratory infection (4.1% each). One participant (2.0%) had an application site reaction (acne), which resolved with no change to study treatment. There were no deaths, SAEs, or TEAEs leading to study treatment interruption or discontinuation.

Critical Appraisal

The main limitation of SCRATCH-AD was the single-arm design. The lack of relevant comparator renders it impossible to draw causal conclusions about comparative efficacy of ruxolitinib 1.5% cream with respect to other treatment options or to vehicle. Interpretation of the changes from baseline is complicated, as they may be due to the intervention, concomitant treatments, a placebo effect, and/or natural history. Additionally, there is a potential risk of bias due to the open-label design. Patients where aware of the treatment and self-reported subjective outcomes, which may have resulted in overestimation of the change from baseline. The

analyses were done in less than 50 patients (safety and mITT populations), which could add the uncertainty to the efficacy results. As SCRATCH-AD was conducted in a single study site located in Quebec, Canada, its study findings generally have a good generalizability to the clinical practice in Canada, except for less-than-ideal representation of Indigenous population in which AD is common.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	• Base case: Patients 12 years of age and older with mild or moderate AD (aligned with the TRuE-AD pivotal trials) • Scenario analysis: Patients 12 years of age and older with moderate AD
Treatment	Ruxolitinib cream
Dose regimen	Applied twice daily to affected skin areas (maximum of 20% BSA for each application) for 8 weeks, and as needed thereafter
Submitted price	$1,075.97 per 100 g tube
Submitted treatment costs	First year: [redacted] per person (based on [redacted] tubes per year)[a] Subsequent years: [redacted] per person (based on [redacted] tubes per year)[a]
Comparator(s)	Base case: • No active treatment[b] Moderate AD scenario: • Abrocitinib • Dupilumab • Upadacitinib
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (50 years)
Key data source	Effectiveness of ruxolitinib cream was informed by the TRuE-AD 1 and TRuE-AD2 trials in the sponsor's base case. In the moderate AD scenario analysis, the effectiveness of abrocitinib, dupilumab, and upadacitinib was informed by the sponsor-conducted NMA.
Key limitations	• Ruxolitinib cream is indicated for patients whose AD is not adequately controlled with topical prescription therapies (TCS, TCI) or when those therapies are not advisable. Efficacy inputs for the sponsor's economic evaluation were obtained from the TRuE-AD 1 and TRuE-AD2 trials, which did not restrict eligibility based on prior treatment experience. Although the sponsor provided subgroup data for patients with a history of TCS and TCI use, these data were not used in the economic model. • The sponsor's base case compared ruxolitinib cream to no active treatment, which is not a relevant comparator for decision making. Clinical expert input received by CDA-AMC for this review noted that patients who do not achieve adequate disease control with topical treatments may try, for example, systemic immunosuppressants (e.g., methotrexate, cyclosporine), or advanced systemic therapies (i.e., abrocitinib, upadacitinib, dupilumab). • It is uncertain whether ruxolitinib cream provides a clinical benefit relative to other treatments for mild to moderate AD due to limitations in the clinical evidence submitted by the sponsor. There have been no head-to-head trials of ruxolitinib cream to any relevant comparator, and the sponsor deemed that an indirect treatment comparison (ITC) for the full indicated population was not feasible. The CDA-AMC clinical review concluded that the submitted ITC for the moderate AD subgroup was insufficient to determine whether ruxolitinib cream would be

Component	Description
	associated with different clinical outcomes relative to abrocitinib, dupilumab, and upadacitinib, owing to methodological limitations and imprecision. • The long-term effectiveness of ruxolitinib cream is highly uncertain owing to a lack of clinical data beyond 52 weeks, and treatment effectiveness waning was not considered by the sponsor. If long-term effectiveness is lower than anticipated, patients who continue to use ruxolitinib cream may require more tubes per year than assumed in the sponsor's analysis, and hence the drug acquisition costs will be higher than predicted. • The sponsor assumed that [redacted] tubes of ruxolitinib cream would be used in the first year of treatment, which is less than would be required based on observations from the TRuE-AD trials ([redacted] tubes, based on mean weight of ruxolitinib cream of [redacted] g in TRuE-AD1 and [redacted] g in TRuE-AD2). Clinical expert input received by CDA-AMC indicated that the amount of ruxolitinib cream required is expected to fluctuate over time based on the frequency and extent of AD flares. • The sponsor assumed that all patients who do not have an adequate treatment response at the end of the 8-week induction period or who later discontinue initial treatment will receive dupilumab as subsequent therapy, which implicitly assumes that patients with mild AD will have progressed to moderate AD after 8 weeks of no active treatment. The cost savings predicted by the sponsor's base case with ruxolitinib cream compared to no active treatment are due to lower drug acquisition costs of subsequent treatment. However, whether any cost savings will be realized in clinical practice is highly uncertain, as there are several agents that are less costly than dupilumab that could be used as subsequent therapy (e.g., immunosuppressants). • In the sponsor's model, from week 12 onward, patients could discontinue ruxolitinib cream or no active treatment on the basis of adverse events or inadequate treatment response. CDA-AMC notes that it is not possible to discontinue no active treatment in practice; discontinuation because of a lack of response is accounted for at week 8 in the model; long-term AEs are unlikely to occur for patients who do not receive active treatment; and discontinuation rates from the 8-week pivotal trials are unlikely to be applicable over the entire 50-year model horizon. • The cost-effectiveness of ruxolitinib cream in adolescents is uncertain. The estimated effectiveness and utility values used in the sponsor's analyses were based on clinical trials that enrolled predominantly adult patients. As noted in the CDA-AMC Clinical Review, this may limit the generalizability of study results to the adolescents in clinical practice. Clinical expert input received by CDA-AMC indicated that adherence to topical treatments may be lower among adolescents, which may affect drug acquisition costs and hence cost-effectiveness estimates.
CDA-AMC reanalysis results	• CDA-AMC undertook reanalyses that addressed some of the identified limitations, including excluding subsequent treatment, aligning the number of ruxolitinib cream tubes in the first year of treatment with observations from the TRuE-AD pivotal trials, and adopting a one-year horizon. CDA-AMC was unable to address the remaining limitations, including uncertainty as to whether the trial population (and hence the cost-effectiveness estimates) adequately reflect the Health Canada indication. • Results suggest that ruxolitinib cream is more costly (incremental costs: $6,747) and more effective (incremental QALYs: 0.04) than no active treatment, resulting in an ICER of $151,361 per QALY gained. A price reduction of at least 68% would be required for ruxolitinib cream to be cost-effective compared to no active treatment at a willingness-to-pay threshold of $50,000 per QALY gained.

AD = atopic dermatitis; AE = adverse event; BSA = body surface area; ICER = incremental cost-effectiveness ratio; IGA = Investigator Global Assessment; ITC = indirect treatment comparison; LY = life-year; QALY= quality-adjusted life-year; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids.

[a] Treatment cost was estimated by the sponsor was based on observations from the TRuE-AD trials (BSA affected by AD, cream used per BSA affected, reduction in BSA affected by AD, and percentage of days on treatment).

[b] In the base case, the sponsor compared ruxolitinib cream to vehicle cream (from the TRuE-AD trials), which contained no active ingredient (i.e., ruxolitinib).

Budget Impact

CDA-AMC identified several key limitations with the sponsor's analysis. The treatment cost of ruxolitinib was underestimated, in that the number of tubes used was not aligned with observations from the TRuE-AD trials. Higher ruxolitinib cream usage in the first year of treatment (compared to subsequent years) was not considered, which underestimated ruxolitinib acquisition costs. The market share and displacement of comparators was uncertain. Prices of comparators paid by public drugs plans were also uncertain.

CDA-AMC reanalysis included aligning the eligible population with the Health Canada indication (mild to moderate AD) and aligning the number of tubes of ruxolitinib cream used in Year 1 with data from the TRuE-AD trials. Based on CDA-AMC reanalyses, reimbursing ruxolitinib cream for use by patients with mild to moderate AD may be cost-saving to the public drug plans (3-year cost-savings of $39,727,424). This estimate was driven by the displacement of dupilumab, which has a higher annual cost than ruxolitinib cream (based on the sponsor's submitted price of ruxolitinib cream and the public list price of dupilumab). However, if the price paid by the public drug plans for dupilumab is at least 32% lower than the public list price, reimbursing ruxolitinib cream for mild to moderate AD will not be cost saving. In the mild AD subgroup, CDA-AMC scenario analysis suggested that reimbursement of ruxolitinib cream was expected to be associated with incremental costs to the public drug plans, given that the more expensive advanced systemic treatments are not indicated for this subgroup, and ruxolitinib cream would displace less costly treatments (e.g., systemic immunosuppressants).

CDEC Information

Members of the Committee:

Dr. Peter Jamieson (Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: November 27, 2024

Regrets:

1 expert committee member did not attend.

Conflicts of interest:

None