CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

CRISABOROLE (EUCRISA — PFIZER CANADA INC.)
Indication: For topical treatment of mild-to-moderate atopic dermatitis in patients two years of age and older

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that crisaborole should not be reimbursed for topical treatment of mild to moderate atopic dermatitis in patients two years of age and older.

Service Line:	CADTH Drug Reimbursement Recommendation
Version:	1.0
Publication Date:	April 2019
Report Length:	7 Pages

CADTH

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

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.

CRISABOROLE (EUCRISA — PFIZER CANADA INC.)

Indication: For topical treatment of mild-to-moderate atopic dermatitis in patients two years of age and older

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that crisaborole should not be reimbursed for topical treatment of mild-to-moderate atopic dermatitis (AD) in patients two years of age and older.

Reasons for the Recommendation

1. Two double-blind randomized controlled trials (RCTs) of patients two years of age and older with mild-to-moderate AD demonstrated that treatment with crisaborole was significantly more likely than the vehicle (i.e., placebo) to achieve an Investigator Static Global Assessment (ISGA scoring) score of 0 to 1 (clear or almost clear) with at least a 2-grade improvement from baseline at Day 29. However, the benefits shown in both RCTs were not compared with standard treatments such as topical corticosteroids (TCS), topical calcineurin inhibitors (TCIs), systemic immunomodulating drugs, or phototherapy. Therefore, there is no direct evidence demonstrating comparative efficacy for crisaborole versus other standard treatments for AD.
2. Both RCTs were not representative of the populations for whom the reimbursement request was made: patients two years and older with mild-to-moderate AD who have failed or are intolerant to a TCS. No evidence related to the reimbursement request population was available in either RCT.
3. The results of both manufacturer-submitted and published network meta-analyses (NMAs) show there were no statistically significant differences found between crisaborole and TCIs (pimecrolimus or tacrolimus) for the proportion of patients achieving ISGA score of 0 to 1 (clear or almost clear). Limitations to the NMAs included the limited number of trials available to inform the network and that only comparisons versus TCIs (pimecrolimus and tacrolimus) were reported. Subgroup analyses based on age were not conducted, the reporting of only one efficacy outcome (achieving an ISGA score of 0 to 1) to assess comparative treatment effects was used in the analysis, and no quantitative assessment of comparative safety was done.

Discussion Points:

- CDEC noted that for patients with mild-to-moderate AD who do not achieve disease control with appropriate skin care measures, the standards of care include TCS and/or TCIs, immunosuppressive drugs, or phototherapy. Based on the availability of other therapies for this condition and the lack of comparative efficacy and safety data, it was felt that crisaborole did not fulfill an unmet need in patients with mild-to-moderate AD.
- CDEC noted that AD is a chronic, relapsing condition where patients often experience episodes of worsening symptoms throughout their life. The submitted trials were limited to treatment during a four-week period; therefore, long-term efficacy and safety data associated with crisaborole are needed.
- CDEC noted the lack of statistical assessment of health-related quality of life measurements in both studies and therefore no conclusions can be drawn in regard to the impact of crisaborole on quality of life.

Background:

Crisaborole received a Health Canada indication for treatment of patients two years of age or older with mild-to-moderate AD. Crisaborole is a phosphodiesterase (PDE)-4 inhibitor. It is available as a topical ointment and the Health Canada-approved dose is to be applied to the affected area in a thin layer, twice daily.

Summary of CDEC Considerations:

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of two double-blind RCTs of crisaborole, a critique of the manufacturer's indirect treatment comparison and pharmacoeconomic evaluation, and a published indirect treatment comparison. CDEC also considered input from clinical experts with experience in treating patients with AD, and patient group-submitted information about outcomes and issues important to patients.

Summary of Patient Input

Two patient groups, the Canadian Skin Patient Alliance (CSPA) and the Eczema Society of Canada (ESC), provided input for this submission. Patient perspectives were obtained from surveys. The following is a summary of key input from the perspective of the patient group(s):

- Although patients with mild-to-moderate AD reported minor overall impact from the disease, patients with moderate-to-severe disease did report interruptions in sleep as well as a negative impact on professional (school, work) and personal life. They also reported infections arising from AD, occurring in 38% of respondents, as well as depression and bullying. Caregivers (parents) reported interruptions in their sleep and anxiety.
- The most common therapies attempted by patients were the TCS, followed by non-medicated preparations. Several other therapies were identified, including the TCIs. Side effects of the TCS identified by the patients included thinning of skin, spider veins, and blistering. Nearly half of all patients (48%) indicated that treatment was uncomfortable and 22% stated it was painful to apply. Cost was also reported as an issue that limited access to therapy in some patients.
- Patient experience with crisaborole was mixed; some patients derived benefit while others did not. Some patients also reported side effects such as pain, burning, or stinging upon application.

Clinical Trials

The systematic review included two double-blind, randomized, placebo-controlled trials of patients with mild-to-moderate AD.

Studies AD-301 (N = 763) and AD-302 (N = 764) were identically designed trials and enrolled patients two years of age and older (with the majority younger than 18 years of age) with mild-to-moderate AD (ISGA scoring) comparing crisaborole in a 2:1 ratio to vehicle during a 28-day treatment course. The primary outcome was the proportion of patients with success by ISGA at Day 29, while secondary outcomes included the proportion of patients with ISGA of clear or almost clear at Day 29, and the time to success in ISGA. There were numerically fewer withdrawals in the crisaborole vehicle versus groups in each of AD-301 (6% versus 12%, respectively) and AD-302 (6% versus 15%).

Limitations of the included trials included the fact that health-related quality of life was not statistically assessed in either included study; therefore no conclusions can be drawn about the impact of crisaborole on quality of life, an important consideration for patients with AD. There were numerically more withdrawals in the vehicle group than with crisaborole, and this difference appears to have been largely accounted for by lack of efficacy. The included trials lacked an active comparator; therefore the relative efficacy of crisaborole to TCS or TCIs is unknown. The included studies had a relatively short duration of follow up and thus long-term efficacy and safety of crisaborole is unknown.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following: proportion of patients achieving success on the ISGA, proportion of patients achieving ‘clear’ or ‘almost clear’ on the ISGA, time to improvement in pruritus, and health-related quality of life. The primary outcome in both trials was the proportion of patients achieving success on the ISGA at Day 29.

- ISGA is a five-point scale that provides a global clinical assessment of AD severity based on an ordinal scale, scored by an investigator or physician ranging from 0 to 4. A score of 0 corresponds to a grade of “clear,” 1 is “almost clear,” 2 is “mild,” 3 is “moderate,” and 4 is “severe” AD. A decrease in score relates to an improvement in signs and symptoms. No minimal clinical importance difference (MCID) is available for ISGA in patients with AD.
- Health-related quality of life was assessed as an exploratory outcome using the dermatology life quality index (DLQI) for adults and the children’s version (CDLQI), as well as the dermatitis family impact questionnaire (DFI). The DLQI is a self-reported, 10-item questionnaire that refers to the preceding week and assesses six different aspects that may affect the quality of life as a result of living with a dermatological condition: symptoms and feelings, daily activities, leisure, work or school, personal

relationships, and side effects of treatment. Each item is scored using a Likert scale that ranges from 0 to 3: a score of 0, 1, 2, and 3 corresponds to the following descriptions of how much an aspect is affected by the disease, respectively: "not at all/not relevant," "a little," "a lot," and "very much." The scores of each of the ten items are summed for an overall DLQI score between 0 and 30 (or a percentage of 30). The MCID is a change in score of at least 3.3 from baseline.

- The DFI questionnaire was designed to assess the impact of disease on the health-related quality of life of parents and families of children affected by AD. It is a disease-specific, self-administered questionnaire that relies on a one week recall, and consists of ten items: housework, food preparation, sleep, family leisure activity, shopping, expenditure, tiredness, emotional distress, relationships, and the impact on the care provider's life due to helping with treatment. Each question is scored on a four-point Likert scale ranging from 0 to 3, for an overall total ranging from 0 to 30 with a higher score corresponding to a greater negative impact on the family's quality of life due to AD. No MCID was identified for the DFI.

Efficacy

The primary outcome in both trials was the proportion of patients achieving success in ISGA at Day 29. Success was defined as ISGA of Clear or Almost Clear with at least a 2-grade improvement from baseline/day 1. For both trials, patients treated with crisaborole were significantly more likely to have achieved "success" on the ISGA as compared with those treated with vehicle (AD-301 = 32.8% vs. 25.4%, *P* value: 0.038 and AD-302 = 31.4% vs. 18.0%; *P* value < 0.001). [redacted]

Health-related quality of life was assessed using the DLQI in both studies, although no statistical tests were performed between comparison groups. In AD-301, the mean (SD) decrease (improvement) from baseline to Day 29 was -5.5 (5.5) for crisaborole and 3.6 (4.6) for vehicle. In AD-302 the mean (SD) decrease from baseline to Day 29 was -5.0 (5.5) for crisaborole and -3.4 (5.8) with vehicle. The MCID for a change from baseline is 3.3, thus clinically significant improvement from baseline was seen in both the crisaborole and vehicle groups.

With respect to the children's DLQI, the mean (SD) reduction from baseline to Day 29 in AD-301 was -5.2 (5.6) with crisaborole and 3.1 (5.9) with vehicle, and in AD-302 was -4.0 (4.9) with crisaborole and -2.9 (5.0) with vehicle.

The mean (SD) reduction (improvement) from baseline to Day 29 in Dermatitis Family Impact (DFI) questionnaire in AD-301 was -3.9 (5.7) with crisaborole and -2.7 (5.6) with vehicle, and in AD-302 it was -3.6 (5.2) with crisaborole and -2.8 (4.8) with vehicle.

The median time to improvement in pruritus was an exploratory end point in both included studies. The median time to improvement in pruritus was 1.32 days with crisaborole and 1.87 days with vehicle (*P* <0.001) in AD-301, and 1.41 days with crisaborole and 1.54 days with vehicle (*P* = 0.425) in AD-302.

Harms (Safety and Tolerability)

- In the AD-301 trial, 1% of patients had a serious adverse event in the crisaborole group versus 0.4% in the vehicle group, and in AD-302 0.6% of crisaborole-treated patients had a serious adverse event versus none with vehicle after 28 days of double-blind treatment in each study. There were no deaths in the study.

- Overall adverse events were similar for crisaborole compared with vehicle (29.4% versus 32.0% of patients, respectively) in AD-302, and there were numerically more patients treated with crisaborole versus vehicle (29.3% versus 19.8%) who had an adverse event in AD-301, after 28 days of double-blind treatment. The most common adverse event was application site pain such as burning or stinging, occurring in 6.2% of crisaborole-treated patients and 1.2% of vehicle-treated patients in AD-301 and 2.7% of crisaborole-treated patients and 1.2% of vehicle-treated patients in AD-302. Application site irritation is a common concern of patients who use topical therapies for AD, according to patient input provided to CDR. Less common (< 1%) AEs in patients treated with crisaborole 2% ointment include contact urticarial. The use of TCIs was related to local symptoms, such as skin burning (burning sensation, stinging, and soreness) or pruritus.

- In AD-301, 1.4% of crisaborole-treated and 0.8% of vehicle-treated patients withdrew due to an adverse event, and in AD-302, 1.0% of crisaborole-treated and 1.6% of vehicle-treated patients withdrew due to an adverse event during the 28-day double-blind phase.
- The relatively short duration (28 days) of the follow-up period in the double-blind comparison phase is unlikely to be of a sufficient duration to assess harms associated with use of crisaborole.

Indirect Treatment Comparisons

Two published NMAs comparing crisaborole with other topical pharmacological therapies were identified and reviewed. Only one outcome, the proportion of patients achieving an ISGA score of 0 to 1, was assessed in the NMAs, and data were only available for the comparison between crisaborole and TCIs (pimecrolimus and tacrolimus). In the manufacturer-submitted NMA, there were no statistically significant differences found between crisaborole and pimecrolimus or tacrolimus for the proportion of patients achieving ISGA score of 0-1 (clear or almost clear). However, both NMAs were limited by the number of trials available to inform the network, only comparisons versus TCIs (pimecrolimus and tacrolimus) reported, subgroup analyses based on age were not conducted, the reporting of only one efficacy outcome (achieving an ISGA score of 0 to 1) to assess comparative treatment effects, and no quantitative assessment of comparative safety. Due to the limitations in the analyses and uncertainty on whether relative treatment effects differ by patient age, no definitive conclusions regarding the comparative efficacy and safety of crisaborole to other topical therapies can be made for either pediatric or adult patients with mild-to-moderate AD.

Cost and Cost-Effectiveness

Crisaborole at 2% is a topical ointment available as a 60 g tube at a submitted price of $138.00. It is recommended for use twice daily and should be applied as a thin layer to all affected areas of skin. In the economic analysis, it was assumed that a 60 g tube would last one month for adults and about five weeks for children.

The manufacturer-submitted a cost-utility analysis comparing crisaborole with TCS (i.e., betamethasone valerate) or TCIs (i.e., pimecrolimus and/or tacrolimus) in patients with mild-to-moderate AD, analyses for children and adults were considered separately. The primary analysis reflected the Health Canada indication in which the comparators were betamethasone valerate and pimecrolimus. Scenario analyses were conducted for the reimbursement-requested indication (i.e., patients who have failed or are intolerant to a topical corticosteroid treatment) in which the comparators were TCIs. In the model, patients received treatment and, after a month, could respond and transition to a controlled disease state; treatment effectiveness was informed by the manufacturer-submitted NMA for the comparison with TCIs and from a published meta-analysis for the comparison with TCS. Otherwise, patients may switch to another line of therapy due to lack of efficacy or adverse events. The manufacturer's base case model was conducted from the perspective of a Canadian publicly funded health-care payer during a one year time horizon for adults and a 15-year time horizon for children. In their deterministic base case, the manufacturer estimated that, for the Health Canada indicated population, the incremental cost-utility ratio (ICUR) of crisaborole compared with betamethasone valerate was $3,956 per quality-adjusted life years (QALY) in children and $44,110 per QALY in adults. For the reimbursement-requested population, crisaborole was associated with ICURs of $721 and 12,435 per QALY in children and adults respectively when compared with tacrolimus. Pimecrolimus was dominated by crisaborole (i.e., crisaborole is less costly and more effective) in all scenarios and in all populations.

CADTH identified the following key limitations with the manufacturer's submitted economic model:

- Relative treatment effects of crisaborole compared with betamethasone valerate is unknown. Given the lack of direct comparative data, the approach to indirectly incorporate clinical efficacy inputs for betamethasone valerate from a meta-analysis that compared, at a class level, TCS to TCI, was considered inappropriate given the heterogeneity noted between clinical studies.
- Given the heterogeneity of the included trials in the manufacturer-submitted NMA, the comparative treatment effects of crisaborole with TCIs remains unclear.
- The approach taken to switch to other lines of therapy in the model appear to favour crisaborole by slowing the progression of the disease severity despite no clinical evidence being available to support such a claim.

- Utilities values for children, by disease severity, were mapped from a published study although the validity of the approach remains unclear.
- The time horizon for adult subgroup analysis was not sufficient given that AD is a chronic illness.

CADTH could not address the limitations related to the uncertainty in relative treatment effects due to the heterogeneity in the manufacturer's NMA. Given the lack of direct and indirect comparative data on betamethasone valerate, the CADTH reanalyses were restricted to TCIs. CADTH's reanalysis assumed disease severity would not worsen, used adult utilities for both populations, and extended to a lifetime time horizon in the adult subgroups. For the Health Canada indication, crisaborole dominated pimecrolimus in children and was associated with an ICUR of $1,333 per QALY in adults. For the reimbursement-requested indication, tacrolimus had higher costs and more QALYs compared with crisaborole; crisaborole was considered cost-effective should a decision-maker be willing to pay less than $24,751 per QALY for children or $15,642 per QALY for adults; otherwise, tacrolimus would be the preferred treatment. Crisaborole is more expensive than betamethasone valerate at a price per gram unit of $2.30 versus $0.09.

CDEC Members:

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

October 17, 2018 Meeting:

Regrets:

One CDEC member did not attend

Conflicts of Interest:

None

March 20, 2019 Meeting:

Regrets:

None

Conflicts of Interest:

None