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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

CRISABOROLE Ointment, 2% (EUCRISA)

(Pfizer Canada Inc.)

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

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Abbreviations

AD	atopic dermatitis
AE	adverse event
CDR	CADTH Common Drug Review
CSPA	Canadian Skin Patient Alliance
HPTCS	high-potency topical corticosteroids
ICUR	incremental cost-utility ratio
ISGA	Investigator's Static Global Assessment
NMA	network meta-analysis
ODB	Ontario Drug Benefit
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RR	relative risk
TCI	topical calcineurin inhibitor
TCS	topical corticosteroids

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Crisaborole (Eucrisa)
Study Question	**Primary Analysis (Health Canada indication):** From the perspective of the publicly funded health care payer, what is the incremental cost-effectiveness of crisaborole compared with available treatments in patients 2 years to 17 years old and in adults with mild-to-moderate atopic dermatitis? **Secondary Analysis (reimbursement requested indication):** From the perspective of the publicly funded health care payer, what is the incremental cost-effectiveness of crisaborole compared with available treatments in patients 2 years to 17 years old and in adults with mild-to-moderate atopic dermatitis who have failed or are intolerant to a topical corticosteroid treatment?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients 2 years of age and older with mild-to-moderate atopic dermatitis. Stratified analyses of age subgroups were conducted for each analysis and are defined as follows: • Children (2 years to 17 years of age) • Adult (age ≥ 18 years)
Treatment	Crisaborole ointment, 2% applied topically, twice daily, to all affected areas of skin
Outcomes	• Quality-adjusted life-years (QALY) • Disease-controlled year
Comparators	**Primary Analysis:** Topical corticosteroid (betamethasone valerate 0.1%) or topical calcineurin inhibitors (pimecrolimus 1%) **Secondary Analysis:** Pimecrolimus 1% or tacrolimus (adults: 0.1%; children: 0.03%)
Perspective	Canadian public health care payer
Time Horizon	• 15 years for children subgroup • 1 year for adult subgroup
Results for Base Case	The manufacturer reported in its deterministic results the following ICUR for crisaborole: **Primary Analysis** • Children subgroup: $3,956 per QALY compared with betamethasone valerate • Adult subgroup: $44,110 per QALY compared with betamethasone valerate **Secondary Analysis** • Children subgroup $721 per QALY compared with tacrolimus • Adults subgroup: $12,435 per QALY compared with tacrolimus In all cases, crisaborole dominated pimecrolimus (i.e., crisaborole was less costly and more effective).
Key Limitations	CADTH identified several key limitations with the submitted analysis: • The relative treatment effect of crisaborole compared with betamethasone valerate is unknown. The manufacturer took a previously published meta-analysis comparing topical corticosteroids to topical calcineurin inhibitors to approximate the relative treatment effects of betamethasone valerate. • Uncertainty exists with the manufacturer's commissioned network meta-analysis for comparative treatment effects of crisaborole to topical calcineurin inhibitors.

Key Limitations	• The approach taken to model switching to other lines of therapy would favour crisaborole. In the model, the line of therapy patients were on would impact their disease severity with worse severity associated with subsequent lines of therapy. Since patients on crisaborole had a lower probability of switching treatments, they were also less likely to progress to a more severe disease. As patient's utilities were based on their disease severity, this may have overestimated benefit with crisaborole. • Utilities values from a published study were arbitrarily mapped to provide an estimate on utility weights at different disease severities in the children subgroup and the validity of the approach taken is unclear. • The time horizon for adult subgroup analysis was not sufficient. Atopic dermatitis is a chronic illness whereas the economic model submitted by the manufacturer only captured the first year of treatment. • The submitted model lacked transparency and was unnecessarily complex. Furthermore, the model has an extremely long run time (ranging from 8 hours to greater than 1 day). This made both the assessment of validity and the ability to conduct reanalysis challenging.
CDR Estimate(s)	CADTH could not address the limitations related to the uncertainty in relative treatment effects due to the clinical uncertainties in the manufacturer's network meta-analysis. CADTH's reanalyses were restricted to TCIs as the approach taken to incorporate betamethasone valerate was considered inappropriate. • For the Health Canada indication, crisaborole dominated pimecrolimus (i.e., crisaborole was less costly and more effective) in children and was associated with an ICUR of $1,333 per QALY in the adult subgroups. • For the reimbursement request indication, tacrolimus had higher costs and more QALYs compared with crisaborole. Crisaborole was considered cost-effective should a decision-maker be willing to pay $24,751 per QALY for children or $15,642 per QALY for adults. Should the decision-maker be willing to pay more, then tacrolimus would be the preferred treatment. Crisaborole is more expensive than betamethasone valerate at a price per gram unit of $2.300 versus $0.0889.

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; TCI = topical calcineurin inhibitor.

Drug	Crisaborole (Eucrisa)
Indication	Crisaborole (Eucrisa ointment, 2 %) is indicated for topical treatment of mild-to-moderate atopic dermatitis in patients two years of age and older
Reimbursement Request	For the treatment of mild-to-moderate atopic dermatitis in patients two years of age and older who have failed or are intolerant to a topical corticosteroid treatment
Dosage Form(s)	Ointment, 2% for topical use
NOC Date	June 7, 2018
Manufacturer	Pfizer Canada Inc.

Executive Summary

Background

Crisaborole 2% ointment (Eucrisa) is indicated for use in patients two years of age and older with mild-to-moderate atopic dermatitis (AD). Crisaborole is a topical ointment that is recommended for use twice daily, and should be applied as a thin layer to all affected areas of skin.[1] The submitted price is $138.00 per 60 g (or $2.300 per g).[2] In the economic analyses, one 60 g tube was assumed to last for one month for adults and about five weeks (one month and 10 days) for children.

The manufacturer submitted a cost-utility analysis comparing crisaborole to topical corticosteroids (TCS, betamethasone valerate 0.1%) or topical calcineurin inhibitors (TCIs, pimecrolimus 1% or tacrolimus [adults: 0.1%; children: 0.03%]). Two subgroups of interest were considered in the economic evaluation, defined by the patient's age (i.e., children two years to 17 years of age and adults 18 years of age and older). The primary analysis reflected the Health Canada indication, with scenario analyses conducted to reflect the submitted reimbursement indication (patients who have failed or are intolerant to a TCS treatment). The manufacturer's base-case model was conducted from the perspective of the Canadian publicly funded health care payer over a one-year time horizon for adults and a 15-year time horizon for children with monthly cycles. Discounting was not applied in the adult subgroup analysis but was applied in the children subgroup with future costs and benefits discounted at 1.5% per annum.[2]

Patients entered the Markov microsimulation on either treatment with crisaborole, TCS, or TCIs. After the first month of treatment, patients may either transition to controlled disease (if treatment response was achieved), or switch to another line of therapy (e.g., high-potency TCS, systemic treatment, phototherapy, or emollients) due to lack of efficacy or adverse events.[2] If treatment response is achieved on the other lines of therapy (with the exception of emollients), patients would then move to the controlled disease health state. Patients in the controlled disease health state can become uncontrolled and would restart the previous treatment that resulted in response.[2,3] Once in the emollients health state, patients were considered to be uncontrolled and remained in this health state until death or the end of the model's time horizon. Children could also transition to an AD resolution health state at any time during the model in which they would be considered cured. Treatment efficacy was based on the manufacturer's submitted network meta-analysis (NMA) for the comparison of crisaborole to TCIs[4] and from a published meta-analysis for the comparison of TCS to TCIs.[5]

Switch patterns (i.e., the treatments patients go on to next following lack of response or adverse events) was informed by Truven claims data from February 2017 through October 2017 held by the manufacturer.[2] Patient's baseline disease severity reflected the crisaborole trials with disease severity reassigned upon entering a new line of therapy. The severity mix associated with each line of therapy was based on the reported baseline characteristics in select clinical studies.[2] Utilities were assigned based on disease control status (i.e., controlled or resolved) or, if patients were on treatment, based on their disease severity (mild, moderate, or severe). Utility weights were obtained from the literature[6,7] and were different for children and adult patients.

The manufacturer's deterministic analysis reported that, for patients with mild-to-moderate AD in the Health Canada indicated population, crisaborole had higher costs and quality-adjusted life-years (QALYs) compared with betamethasone valerate, with an incremental cost-utility ratio of $3,956 per QALY in children and $44,110 per QALY in adults.[2] In patients with mild-to-moderate AD who have failed or are intolerant to TCS (reimbursement request), the manufacturer reported that crisaborole was the cost-effective alternative at a cost-effectiveness threshold greater or equal to $721 in children or less than $12,435 per QALY in adults.[2] Pimecrolimus was dominated by crisaborole in all scenarios (i.e., crisaborole is less costly and more effective).

Summary of Identified Limitations and Key Results

CADTH identified several key limitations with the model submitted by the manufacturer. The key limitation was the reliance on indirect estimates of the comparative clinical efficacy for crisaborole. There was limited evidence to inform the relative efficacy of betamethasone valerate compared with crisaborole, and the approach taken to derive relative treatment efficacy inputs was considered inappropriate as it did not take into account the potential heterogeneity between clinical studies. Furthermore, considerable heterogeneity was found between the limited clinical studies in the manufacturer's NMA, leading to uncertainty with respect to the relative efficacy and harms of crisaborole to TCIs. Furthermore, as patient's disease progression was dependent on treatment, this led to unlikely disease progression as per the clinical experts consulted as part of this review. According to the clinical experts, disease severity would impact treatment choice rather than the contrary. Although the utility values used for children were from a published utility elicitation study,[6] the selection of the health-state description to correspond to the model's disease severity utility values were not well supported. CADTH guidelines recommend that the time horizon of a model be sufficiently long to capture all differences in costs and health effects between treatments.[8] Despite AD being a chronic disease, the manufacturer only modelled the adult population for one year without appropriate justification for the truncated time horizon. Lastly, the model has an extremely long run time (ranging from eight hours to greater than one day). This limited CADTH's ability to run additional analyses.

There is significant uncertainty in the true cost-effectiveness of crisaborole given the uncertainty on the relative treatment effects from the lack of direct comparisons. Rather, indirect evidence was taken to estimate relative treatment efficacy. The manufacturer's NMA included a limited number of studies that only compared crisaborole with TCIs with clinical heterogeneity noted across the included studies. CADTH could not address the limitations related to relative treatment effects. Furthermore, CADTH's reanalyses were restricted to TCIs as the approach taken to incorporate treatment effects for betamethasone valerate was considered inappropriate. CADTH reanalyses attempted to address the remaining limitations by assuming patient severity did not change as a result of the line of therapy patients

switched to. Furthermore, in the children subgroup analyses, utility values were set to be the same as those used for adults. In the adult subgroup analyses, the time horizon was extended to lifetime.

Conclusions

The CADTH reanalyses found that, for children, crisaborole dominated pimecrolimus (i.e., crisaborole was less costly and more effective than pimecrolimus) in the Health Canada–approved population. For the reimbursement population in which tacrolimus was also considered, crisaborole was found to be less costly and less effective. Where a decision-maker is willing to pay more than $24,751 per QALY, tacrolimus would be considered cost-effective.

In the adult population, the incremental cost-utility ratio for crisaborole compared with pimecrolimus was $1,333 per QALY gained for the Health Canada–approved indication. In the reimbursement population, crisaborole was less costly and less effective compared with tacrolimus. Crisaborole would be considered cost-effective under a willingness-to-pay threshold of $15,642 per QALY. Where a decision-maker is willing to pay more than $15,642 per QALY, tacrolimus would be considered cost-effective.

It should be noted that there is a lack of comparative effectiveness data between crisaborole versus TCIs, suggesting that the interpretation of the results may warrant careful interpretation as the true cost-effectiveness of crisaborole is uncertain. Similarly, the potential economic value of crisaborole compared with TCS remains unclear given the paucity of comparative clinical evidence. The drug cost of crisaborole ($2.30 per gram) is greater than betamethasone valerate ($0.0889 per gram).

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's PE Submission

The manufacturer submitted a cost-utility analysis comparing, in the primary analysis, crisaborole to betamethasone valerate and pimecrolimus in children and adults with mild-to-moderate atopic dermatitis (AD) as per the Health Canada–approved indication. Betamethasone valerate 0.1% was used to represent mild topical corticosteroids (TCS) because it had the highest use in a national public claims database and because of its relatively low cost compared with other TCS. Pimecrolimus 1% was included because it is the only topical calcineurin inhibitor (TCI) approved for use in mild-to-moderate AD. A secondary analysis was undertaken in children and adults with mild-to-moderate AD whose disease was not adequately controlled with TCS therapies, reflecting the reimbursement requested population. In this analysis, crisaborole was compared with both pimecrolimus 1% and tacrolimus (adults: 0.1%; children: 0.03%) as both treatments are currently indicated in this population.[2,9,10] Children (two years to 17 years of age) and adult (18 years of age or older) subgroups were defined with subgroup analyses conducted in all analyses.[2] The starting age of patients entering in the model was two years old and 18 years old, respectively, in the children and adult models. The distribution of baseline disease severity in the model reflected the crisaborole trials (i.e., AD-301 and AD-302) and consisted of 38.5% mild and 61.5% moderate AD patients.[2,11,12] The model was based on monthly cycles and adopted a 15-year time horizon for children (discounting of both costs and clinical outcomes at 1.5%) and a one-year time horizon for adults (no discounting performed). Base-case analyses were undertaken from the perspective of the publicly funded health care payer.[2]

The manufacturer submitted an individual-level state-transition (Markov) model with treatment and disease-specific health states defined.[2] Patients with mild-to-moderate AD started the model taking crisaborole or one of its comparators (TCS or TCIs). After one month, patients could respond to treatment and go into a controlled disease health state whereby they were no longer on treatment, or discontinue due to lack of efficacy or adverse events and switch to a subsequent line of treatment (i.e., high-potency topical corticosteroids [HPTCS], systemic therapy or phototherapy, or emollients). Treatment efficacy, in terms of disease control, was defined as response on the Investigator's Static Global Assessment (ISGA) score of 0 to 1 at day 28 to 29 and came from the manufacturer's submitted network meta-analysis (NMA) and a meta-analysis that compared TCS to TCIs. Patients on HPTCS, systemic therapy, or phototherapy could also be on concomitant crisaborole, TCS, and/or TCIs. Patients on HPTCS may further switch to systemic therapy/phototherapy or emollients while patients receiving systemic therapy/phototherapy can only switch to emollients if they do not achieve treatment response. With the exception of the emollients health state, patients in the other treatment-specific health states may respond to their treatment and move to the controlled disease health state. The manufacturer's model assumed that once in the emollients health state, patients were assumed to be uncontrolled and remained in this health state until death or the end of the model's time horizon as other treatment options were considered exhausted and[2] patients could not return to a prior line of therapy if they had history of failure within that line of therapy. Patients in the controlled disease health state have a probability of relapsing that was based on the severity of their disease prior to their last treatment response and, upon relapse, patients would re-initiate the treatment that

they last responded to.[2] The model structure for children also included an AD resolution health state to incorporate the possibility that children could be cured of AD and not be at further risk of AD relapse.[2]

Patients' disease severity over time changed according to which line of therapy they were on. For instance, a patient with mild disease severity who did not respond to initial treatment after one month of treatment could then switch to HPTCS and have a probability of [redacted] of being moderate AD and [redacted] probability of being severe AD whereas, if the patient switched to systemic therapy, they would have a 20% and 80% probability of having moderate AD and severe AD, respectively (Table 11 in Appendix 4). As the manufacturer assumed no mortality effect of treatment, all treatment-related benefits were captured by an improvement in health-related quality of life. Utilities were based on the disease control status (i.e., controlled or resolved), or, if the patient was on treatment, their level of disease severity (i.e., mild, moderate, severe). Utilities were specific to children and adults. These were derived from the published literature.[6,7,13,14] The model assumed no decrement in utility due to adverse events (AEs).[2]

The model included acquisition costs of crisaborole, other treatment costs (HPTCS, systemic therapy, phototherapy), and physician visit costs. Drug costs of crisaborole, TCS, and TCIs were based on an assumption that adults would use 60 g per month and children would use 45 g per month.[2] As all patients were assumed to receive emollients as background therapy unless AD resolved, the cost of emollients was assumed to be equal across treatment health states. The cost of crisaborole was provided by the manufacturer[2] and the costs of other drugs came from the Ontario Drug Benefit (ODB) Formulary[15] when possible or from a national database (i.e., IQVIA 2018).[2]

Manufacturer's Base Case

The base-case sequential analyses reported by the manufacturer were deterministic and represent the result of 10,000 patients.

In the primary analysis representing the Health Canada indication, crisaborole was found by the manufacturer to be $147 more expensive than betamethasone valerate for children. The estimated benefit of crisaborole was an additional 0.04 QALYs compared with betamethasone valerate over 15 years. Table 12 shows the contribution of the different sources of cost to the overall total costs. Crisaborole was more costly than both treatments but resulted in other medical costs being lower. This resulted in crisaborole having an incremental cost-utility ratio (ICUR) of $3,956 per QALY gained compared with betamethasone valerate.[2]

In the primary analysis for adults, the manufacturer reported that crisaborole was $182 more expensive than betamethasone valerate. The estimated benefit of crisaborole in the adult population was an additional 0.004 QALYs over one year for betamethasone valerate. The ICUR for crisaborole was $44,110 per QALY compared with betamethasone valerate (Table 2).[2]

In the secondary analysis that reflects the reimbursement requested indication, crisaborole was found by the manufacturer to be $7 more expensive than tacrolimus for children. The estimated benefit of crisaborole over 15 years was an additional 0.01 QALYs compared with tacrolimus. This resulted in crisaborole having an ICUR of $721 per QALY (Table 3). [2]

In the secondary analysis for adults, crisaborole was found by the manufacturer to be $6 less expensive than tacrolimus. The estimated benefit of crisaborole over a year was 0.001 fewer QALYs compared with tacrolimus. Tacrolimus would be the cost-effective option if the cost-effectiveness threshold exceeded $12,435 per QALY (Table 3).[2]

In all cases, crisaborole dominated pimecrolimus (i.e., crisaborole was less costly and more effective). Detailed results can be found in Table 12 and Table 13 of Appendix 4.

Table 2: Summary of Deterministic Results of the Manufacturer's Base Case — Primary Analysis

	Expected QALY	Expected Costs ($)	Incremental QALYs	Increments Costs ($)	Sequential ICUR ($/QALY)
Children Subgroup					
Betamethasone valerate	10.85[a]	2,596			
Crisaborole	10.89[a]	2,743	0.04	147	3,956
Pimecrolimus	10.87[a]	2,746	–0.02	3	Dominated
Adult Subgroup					
Betamethasone valerate	0.81	581			
Crisaborole	0.81	763	0.004	182	44,110
Pimecrolimus	0.81	775	–0.002	12	Dominated

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] Corrected. The manufacturer's pharmacoeconomic report appears to have presented life-years gained.

Source: Manufacturer's pharmacoeconomic submission.[2]

Table 3: Summary of Deterministic Results of the Manufacturer's Base Case — Secondary Analysis

	Expected QALY	Expected Costs ($)	Incremental QALYs	Increments Costs ($)	Sequential ICUR ($/QALY)
Children Subgroup					
Tacrolimus	10.90	2,738			
Crisaborole	10.91	2,745	0.01	7	721
Pimecrolimus	10.88	2,748	–0.02	3	Dominated
Adult Subgroup					
Crisaborole	0.81	757			
Tacrolimus	0.81	763	0.001	6	12,435[a]
Pimecrolimus	0.81	770	–0.003	7	Dominated

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] Tacrolimus is the cost-effective option at a cost-effectiveness threshold greater than $12,435 per additional QALY.

Source: Manufacturer's pharmacoeconomic submission.[2]

Summary of Manufacturer's Sensitivity Analyses

Uncertainty was addressed using probabilistic analysis, one-way deterministic sensitivity analyses, and scenario analyses.[2] Based on the manufacturer's one-way deterministic sensitivity analyses, the results of the analyses for children were most sensitive to the relative treatment effect of TCIs, the modelled time horizon, and the utility of the severe health state. The results of the analyses in the adult population were similar in that the model was most sensitive to the same set of inputs and assumptions and, additionally, the

utility values in the controlled health state.[2] The uncertainty in the relative treatment effects of TCS was not tested in sensitivity analyses.

Scenario analyses were used to consider a broader societal perspective and the amount of topical drugs used based on a claims analysis. Adopting a broader societal perspective by including indirect costs resulted in crisaborole being less expensive than pimecrolimus and betamethasone valerate, but tacrolimus remained less expensive compared with crisaborole. As the cost difference was not as large, the results remained robust and did not change the overall conclusions.[2] Modelling the amount of topical drugs used based on another claims analysis[2] similarly had a small effect on the results and did not change the conclusions.

The manufacturer only reported pairwise probabilistic sensitivity analyses at a willingness-to-pay of $100,000 per QALY for the secondary analysis. The manufacturer reported that crisaborole for children has a 0.81 and 0.60 probability of being the cost-effective treatment compared with pimecrolimus and tacrolimus, respectively, and that crisaborole for adults had a 0.71 and 0.47 probability of being the cost-effective option compared with pimecrolimus and tacrolimus, respectively.

The results of these analyses suggest that parameters pertaining to the relative treatment effect had the largest impact on the ICUR.

Limitations of Manufacturer's Submission

1. Limited evidence on the relative efficacy of betamethasone valerate to crisaborole: As the clinical trials on crisaborole were vehicle-controlled trials,[16] relative treatment efficacy was informed from indirect treatment comparisons. Although the manufacturer's submitted NMA included all topical pharmacological therapies as relevant comparators of interest, only nine randomized controlled trials (RCTs) were identified that have studied crisaborole, TCIs (pimecrolimus and tacrolimus), and vehicle control.[4] To incorporate the potential treatment effectiveness of betamethasone valerate to crisaborole, the manufacturer's model took a previously published meta-analysis that compared, at a class level, TCS to TCIs.[5] Specifically, relative treatment effects were first calculated for pimecrolimus by combining the reported relative risk (RR) (i.e., [redacted]) for response from the manufacturer's submitted NMA with the probability of response for crisaborole (i.e[redacted]) and then, to determine the probability of treatment response for betamethasone valerate, the manufacturer's model combined the calculated probability of response for pimecrolimus by the RR of TCS compared with TCIs that was reported in the meta-analysis.[5] The approach taken does not adequately account for potential differences in heterogeneity between clinical studies. This is particularly important as only one of the trials included in the meta-analysis by Broeders et al. was conducted in patients with mild-to-moderate AD with the remaining studies conducted in patients with more severe forms of AD.[5] This was different from the manufacturer's NMA that was specific to patients with mild-to-moderate AD and suggests that there is substantial clinical heterogeneity between the meta-analysis and the manufacturer's NMA. Furthermore, in applying the RR to the probability of treatment response for pimecrolimus, this may have biased against betamethasone valerate. The meta-analysis by Broeders combined all TCIs together as a class, suggesting that there are no differences in treatment response within this drug class whereas the manufacturer's model selected tacrolimus which had a lower probability of disease control compared with tacrolimus (i.e., [redacted][pimecrolimus]

versus [redacted][tacrolimus]). By anchoring the RR to the lower estimate, this would similarly reduce the relative efficacy estimated for betamethasone valerate.

Given the lack of evidence on the comparative clinical efficacy between crisaborole and betamethasone valerate, CADTH reviewers considered the approach taken by the manufacturer to be inappropriate and to have likely introduced bias. As such, the CADTH reanalysis was unable to compare crisaborole to betamethasone valerate in order to determine the relative cost-effectiveness between these two interventions.

2. Reliance on data from the NMA: There is no direct evidence of the relative effectiveness of crisaborole versus TCIs and thus, comparative efficacy inputs were sourced from a manufacturer-commissioned NMA.[4] As indicated in the CADTH Common Drug Review (CDR) clinical review, there are uncertainties in the results of the indirect treatment comparison arising from between-study heterogeneity that may not have been adequately controlled. Further, longer-term comparative efficacy data from RCTs were lacking and the NMA did not consider comparative safety.
3. Disease severity based on treatment: In the manufacturer's model, patient disease severity (i.e., mild/moderate/severe) is attributed to their treatment assignment. Of the patients starting in the model, 38.5% of patients began with mild AD and 61.5% began with moderate AD, to reflect the average baseline disease severity reported in AD-301 and AD-302.[11,12] If a patient switched to another line of therapy, regardless of the reason for treatment switching, the treatment assignment would dictate that the patient's disease severity be reassigned. The reassignment of disease severity by treatment was based on the baseline disease severity reported in select clinical studies.[16-21] According to the clinical experts consulted on this review, the assignment of disease severity according to treatment led to unrealistic patient disease progression. For instance, the model permitted a large portion of patients who did not respond to treatment to progress from mild to severe AD in one month. Similarly, after the first month of treatment, as the model only permitted patients on phototherapy to remain in the mild disease state (e.g., 15.8% of patients on phototherapy remain mild and [redacted] of non-responders switch to phototherapy), this meant that [redacted] and [redacted] of those starting crisaborole or TCS respectively who were non-responders in the first month remained in the category of mild AD severity with the remaining patients who were non-responders considered to have moderate-to-severe AD. This approach favours treatments with lower rates of switching (either due to achieving response or because they are associated with fewer adverse effects) as it would slow the progression of the disease severity of AD. This is not substantiated by the clinical evidence as there is no evidence suggesting that crisaborole slows the severity of disease compared with alternative treatment. CDR undertook a more conservative reanalysis that assumed patient disease severity does not change.
4. Utility value for children: Limited information was available to estimate disease-specific utility values for children with AD. Parameters were obtained from a study that took four out of 45 items that were surveyed from parents considered to impact "child-centred" quality of life (i.e., activities, mood, settled, sleep) and, when described on two levels (being impacted or not), resulted in a descriptive system describing 16 health states. These health states were then scored on a preference-based measure of quality of life for AD.[13] In the manufacturer's model, mild AD was taken as the average of the median scores of health states associated with none or one decrement, moderate as the average of the median scores of health states associated with two or three decrements and severe was assumed to be the average of the median scores of health states associated with three or four decrements.[6] This resulted in children with severe AD

having a utility of 0.59. This suggests that children are willing to give up 41% of their time alive to go from severe AD to perfect health. The utility values used in children were much lower than those collected in an adult trial (i.e., 0.76 for severe AD in adults). As the mapping of utilities to disease severity was not well justified, CADTH selected the utilities used in the adult population to reflect those in the pediatric population.

5. Model time horizon: CADTH guidelines recommend that the time horizon of a model be sufficiently long to capture all differences in costs and health effects between treatments.[8] Despite AD being a chronic disease, the manufacturer only modelled the adult population for one year, whereas for the pediatric population a longer time horizon was selected (i.e., up to the age of 18). It is not clear why a shorter time horizon was selected for the adult subgroup analyses and CADTH extended the time horizons to a lifetime in order to align with CADTH guidelines.
6. Clinical trial does not reflect reimbursement indication: Clinical data for the populations for which the manufacturer is seeking reimbursement are limited. The submitted pharmacoeconomic analysis was based on an NMA that considered a broader patient population i.e., the Health Canada indication. Therefore, cost-effectiveness of crisaborole based on the submitted model is highly uncertain in the population that has failed or is intolerant to TCS.
7. Lack of transparency and functionality of the manufacturer's submitted model: The submitted model had several issues that made validation and evaluation challenging. The original model did not allow for all comparators to be run simultaneously although this was later provided to CADTH following a request for additional information to the manufacturer. However, in responding to this request, two versions of the model were submitted to CADTH by the manufacturer. Of note, the second version of the model submitted to CADTH on August 2nd was found to have notably unstable results. The source of the instability remains unclear. The coding used in modelling was overly complicated and lacked transparency. Furthermore, the model run time was extremely long (ranging from eight hours to more than one day), which limited CADTH's ability to test scenarios.

CADTH Common Drug Review Reanalyses

All CDR reanalyses entailed revising comparator pricing to reflect per-unit prices based on the ODB Formulary as of July 2018. While the manufacturer did not specify when they cited ODB for their drug costs, changes were made to ODB Formulary list prices in April 2018. The results of the CDR reanalysis are reported in Table 4 and Table 5. The reanalysis addressed the limitations identified above by:

- limiting the comparison of crisaborole to pimecrolimus (primary analysis) and to both pimecrolimus and tacrolimus (secondary analysis), given that relative efficacy and safety data were available from a manufacturer's submitted NMA[4]
- using adult utilities for both populations
- eliminating the possibility of severity progression in the overall economic model
- using a lifetime horizon in the adult subgroup.

Compared with the manufacturer's results, the CADTH reanalysis (consisting of 1,000 runs of 10,000 patients) resulted in higher costs and higher QALYs for all comparators for adults and similar costs and higher clinical effects for children. For the children subgroup, crisaborole dominated pimecrolimus (i.e., crisaborole was less costly and more effective)

but, when considering tacrolimus, crisaborole produced fewer QALYs at a lower cost, resulting in an ICUR for tacrolimus of $24,751 per QALY (Table 4). Similar findings were noted in the adult subgroup as crisaborole dominated pimecrolimus but was less effective and less costly compared with tacrolimus (the ICUR for tacrolimus was $15,642 per QALY).

As noted, there is considerable uncertainty in terms of the comparative clinical efficacy of betamethasone valerate to crisaborole given that the manufacturer's NMA did not identify any studies on TCS to be included in their NMA.[22] CADTH reanalyses removed this comparator, although an exploratory reanalysis with betamethasone valerate as a comparator using the manufacturer's approach to incorporate the relative treatment effects can be found in Appendix 4 (Table 14).

Table 4: CADTH Reanalysis of Limitations — Primary Analysis

	Scenario	Treatments	QALYs	Cost	ICUR (per QALY)
	Base Case for Children, Submitted by Manufacturer (Deterministic)	Crisaborole	10.89	$2,743	
		Pimecrolimus	10.87	$2,746	Dominated
1.1[a]	Updated costs	Pimecrolimus	10.803	$2,757	
		Crisaborole	10.787	$2,762	Dominated
2.1[a]	Adult utilities	Crisaborole	11.772	$2,765	
		Pimecrolimus	11.765	$2,771	Dominated
3.1[a]	No progression	Crisaborole	11.350	$2,398	
		Pimecrolimus	11.340	$2,403	Dominated
4.1[b]	CADTH reanalysis	Crisaborole	12.094	$2,143	
		Pimecrolimus	12.091	$2,143	Dominated
	Base Case for Adults, Submitted by Manufacturer (Deterministic)	Crisaborole	0.81	$763	
		Pimecrolimus	0.81	$775	Dominated
1.1[a]	Updated costs	Crisaborole	0.811	$753	
		Pimecrolimus	0.809	$765	Dominated
2.1[ab]	Lifetime horizon	Pimecrolimus	31.796	$13,429	
		Crisaborole	31.801	$13,434	$1,000
3.1[a]	No progression	Crisaborole	0.820	$720	
		Pimecrolimus	0.819	$731	Dominated
4.1[b]	CADTH reanalysis	Pimecrolimus	32.814	$11,658	
		Crisaborole	32.817	$11,662	$1,333

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] Indicates those scenarios included in the CDR base-case reanalysis.

[b] Deterministic analysis run due to length of time to run analysis (approximately 14 hours).

Table 5: CADTH Reanalysis of Limitations — Secondary Analysis

	Scenario	Treatments	QALYs	Cost	ICUR (per QALY)
	Base Case for Children, Submitted by Manufacturer (Deterministic)	Tacrolimus	10.90	$2,738	–
		Crisaborole	10.91	$2,745	$721
		Pimecrolimus	10.88	$2,748	Dominated
1.2[a]	Updated costs	Tacrolimus	10.810	$2,751	–
		Crisaborole	10.811	$2,753	$1,658
		Pimecrolimus	10.794	$2,759	Dominated
2.2[a]	Adult utilities	Tacrolimus	11.780	$2,756	–
		Crisaborole	11.780	$2,756	$5,629
		Pimecrolimus	11.773	$2,762	Dominated
3.2[a]	No progression	Tacrolimus	11.344	$2,404	–
		Crisaborole	11.346	$2,404	$63
		Pimecrolimus	11.335	$2,409	Dominated
4.2[b]	CADTH reanalysis	Crisaborole	11.957	$2,391	–
		Pimecrolimus	11.951	$2,395	Dominated
		Tacrolimus	11.957	$2,399	$24,751
	Base Case for Adults, Submitted by Manufacturer (Deterministic)	Crisaborole	0.81	$757	–
		Tacrolimus	0.81	$763	$12,435
		Pimecrolimus	0.81	$770	Dominated
1.2[a]	Updated costs	Tacrolimus	0.810	$744	–
		Crisaborole	0.809	$755	Dominated
		Pimecrolimus	0.807	$768	Dominated
2.2[ab]	Lifetime horizon	Pimecrolimus	31.865	$13,468	–
		Crisaborole	31.869	$13,472	$1,056
		Tacrolimus	31.879	$13,484	$1,267
3.2[a]	No progression	Tacrolimus	0.826	$713	–
		Crisaborole	0.825	$718	Dominated
		Pimecrolimus	0.824	$730	Dominated
4.2[b]	CADTH reanalysis	Pimecrolimus	32.733	$11,611	–
		Crisaborole	32.736	$11,621	$3,606
		Tacrolimus	32.738	$11,648	$15,642

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] Indicates those scenarios included in the CDR base-case reanalysis.

[b] Deterministic analysis run due to length of time to run analysis (approximately 14 hours).

In light of the economic findings of the primary analyses, a price reduction analysis was not conducted. A price reduction analysis (Table 6) was only conducted for the secondary analysis, which demonstrated that, in adult patients, a 15% reduction in price when compared with tacrolimus and a 5% price reduction in pediatric patients would be required to bring the ICUR to $50,000 per QALY.

Table 6: CADTH Reanalysis Price Reduction Scenarios for the Secondary Analysis

ICUR of Crisaborole Versus Tacrolimus and Pimecrolimus (Cost per QALY)		
Price Reduction	**Base-Case Analysis Submitted by Manufacturer[a]**	**Reanalysis by CADTH (Based on CADTH Base Case)**
Children		
Submitted	Tacrolimus < $721 Crisaborole ≥ $721	Crisaborole < $24,751 Tacrolimus ≥ $24,751
5%[a]	Crisaborole dominates	Crisaborole dominates
10%[a]	Crisaborole dominates	Crisaborole dominates
Adults		
Submitted	[a]Crisaborole < $12,435 Tacrolimus ≥ $12,435	Pimecrolimus < $3,606 Crisaborole > $3,606 and < $15,642 Tacrolimus ≥ $15,642
5%[a]	Crisaborole < $15,694 Tacrolimus ≥ $15,694	Crisaborole < $39,588 Tacrolimus ≥ $39,588
10%[a]	Crisaborole < $48,799 Tacrolimus ≥ $48,799	Crisaborole < $41,835 Tacrolimus ≥ $41,835
15%[a]	Crisaborole < $76,359 Tacrolimus ≥ $76,359	Crisaborole < $109,866 Tacrolimus ≥ $109,866

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] Deterministic analyses.

Issues for Consideration

- The clinical experts consulted on this review noted that there are no clear and objective definitions of response. The clinical expert stated that the Eczema Area and Severity Index (EASI) score is more likely to be used to define response to treatment in a clinical setting.
- CADTH was unable to assess the impact of potentially lower prices of comparators on the economic results. Thus, it is unknown if the reduced effective price of comparators would lead to differing conclusions than the current analysis that is based on the list prices of the branded drugs.
- The manufacturer selected betamethasone valerate to represent the class of TCS as it is the most commonly prescribed TCS for AD in Canada, which was also confirmed by the clinical experts consulted by CADTH. Furthermore, betamethasone valerate is associated with the lowest list price amongst TCS and selecting this as the comparator may provide the most conservative estimate. However, given the confidential nature of the negotiated effective price for pharmaceuticals, CADTH was unable to assess the impact of potentially lower prices for other TCS on the results. If the effective price of other TCS is lower than betamethasone valerate, this may lead to differing conclusions than the current analysis.
- According to the clinical experts consulted on this review, concomitant treatment is often prescribed in clinical practice given that the choice of treatment depends on the areas of skin affected.[23] For large body surface areas TCS are commonly prescribed, whereas TCIs are more commonly prescribed for more sensitive skin sites (e.g., face, skin folds).

Patient Input

Patient input gathered by the Canadian Skin Patient Alliance (CSPA) and the Eczema Society of Canada were obtained from surveys of North American patients and caregivers.

Specifically, the CSPA survey reported the result by disease severity and large differences in patient impact on daily living were reported between mild and moderate AD symptoms. This highlights the importance of evaluating treatments in mild and moderate patients separately. Patients with mild AD reported minor impact, with some not requiring medicated treatment, whereas in patients with moderate-to-severe AD, the condition had a greater impact on both the lives of patients and their caregivers (i.e., interrupted sleep, impacts of mental wellbeing, negative effects on work, school, and personal life).

AEs were reported as an important consideration in using treatment that affected adherence to therapy, particularly in children. Patient surveys reported a much higher proportion of patients affected by AEs than were used in the models. The CSPA survey of US patients with experience with crisaborole reported that 83% of patients reported experiencing pain, burning, or stinging with application, whereas the model assumed discontinuation associated with crisaborole was the lowest compared with other treatment alternatives (monthly discontinuation rate: 1.2%). The model did not account for the effect of AEs on quality of life or for how AEs may impact treatment compliance outside of treatment discontinuation.

It was also reported that the experience with crisaborole was similar to other treatments that had been used by patients in terms of effectiveness and ease of use. This statement was supported by the model, which found little difference in treatment effects between treatments.

Conclusions

The CADTH reanalyses found that, for children, crisaborole dominated pimecrolimus (i.e., crisaborole was less costly and more effective than pimecrolimus) in the Health Canada–approved population. For the reimbursement population in which tacrolimus was also considered, crisaborole was found to be less costly and less effective; where a decision-maker is willing to pay more than $24,751 per QALY, tacrolimus would be considered cost-effective.

In the adult population, the ICUR for crisaborole compared with pimecrolimus was $1,333 per QALY gained for the Health Canada–approved indication. In the reimbursement population, crisaborole was less costly and less effective compared with tacrolimus. Crisaborole would be considered cost-effective under a willingness-to-pay threshold of $15,642 per QALY; where a decision-maker is willing to pay more than $15,642 per QALY, tacrolimus would be considered cost-effective.

It should be noted that there is a lack of comparative effectiveness data between crisaborole versus TCIs suggesting that the interpretation of the results may warrant careful interpretation as the true cost-effectiveness of crisaborole is uncertain. Similarly, the potential economic value of crisaborole compared with TCS remains unclear given the paucity of comparative clinical evidence. The drug cost of crisaborole ($2.30 per gram) is greater than betamethasone valerate ($0.0889 per gram).

Appendix 1: Cost Comparison

The comparators presented in Table 7 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 7: CADTH Cost Comparison Table of Topical Corticosteroids for Atopic Dermatitis

Drug/Comparator	Strength and Form	Package Size	Price per Package ($)	Recommended Dose	Price per Gram/mL ($)
Topical PDE4 Inhibitor					
Crisaborole (Eucrisa)	2% ointment	60 g tube	$138.00[a]	Thin layer twice daily to affected areas.	2.3000[a]
Topical Corticosteroids					
Amcinonide (generics)	0.1% cream	60 g tube	11.73	Thin amount to affected area twice daily, max 5 days on face, axillae, scrotum, or scalp, two to three weeks elsewhere.	0.1955
	0.1% lotion	60 mL bottle	15.60		0.2600
	0.1% ointment	60 g tube	15.00		0.2500
Betamethasone dipropionate (generic)	0.05% cream	50 g tube	10.24	Thin film to affected area twice daily. Duration of therapy varies; need should be reassessed at least every 4 weeks.	0.2048
	0.05% lotion	75 mL bottle	14.85		0.1980
	0.05% ointment	50 g tube	10.76		0.2152
Betamethasone valerate (generic)	0.1% cream	450 g jar	40.00[b]	No recommended daily dose. Use as directed by clinicians.	0.0889
	0.1% lotion	30 mL bottle 60 mL bottle	9.38 18.75		0.3125
	0.1% scalp lotion	75 mL bottle	6.40		0.0853
	0.1% ointment	450 g jar	40.00[b]		0.0889
Clobetasol propionate (generic)	0.05% cream	15 g tube 50 g tube 450 g jar	3.42 11.40 102.55[b]	Thin amount to affected area twice daily. Weekly application should not exceed 50 g, and limited to two consecutive weeks.	0.2279
	0.05% scalp lotion	20 mL 60 mL	3.98 11.94		0.1990
	0.05% ointment	15 g tube 50 g tube	3.42 11.40		0.2279
Desonide (generic)	0.05% cream	15 g tube 60 g tube 454 g jar	3.98 15.90 120.31[b]	Thin amount to affected area twice daily, may be increased in refractory cases.	0.2650
	0.05% ointment	15 g tube 60 g tube 454 g jar	3.97 15.88 120.17[b]		0.2647
Desoximetasone (Topicort)	0.25% cream	20 g tube 60 g tube	14.25 42.76	Thin amount to affected area twice daily.	0.7127[c]
	0.25% ointment	60 g tube	41.60		0.6934[c]
Fluocinonide (Lyderm, Lidex)	0.05% cream	15 g tube 60 g tube 400 g jar	3.57 14.27 95.12[b]	Thin amount to affected area twice daily. Weekly application should not exceed 45 g, and limited to two weeks.	0.2378
	0.05% gel	15 g tube 60 g tube	4.61 18.46		0.3076
	0.05% ointment	15 g tube 60 g tube	4.54 18.15		0.3035

Drug/Comparator	Strength and Form	Package Size	Price per Package ($)	Recommended Dose	Price per Gram/mL ($)
Fluocinonide (Tiamol)	0.05% emol cream	25 g tube 100 g jar	4.95 19.80	Thin amount two to four times daily.	0.1980
Halobetasol propionate (Ultravate)	0.05% cream	15 g tube 50 g tube	16.21 54.03	Thin amount to affected area twice daily, limited to 50 g weekly and two weeks without re-evaluation.	1.0806[d]
	0.05% ointment	15 g tube 50 g tube	15.74 52.48		1.0495[d]
Hydrocortisone (various)	0.5% cream	45 g tube	6.00	No recommended daily dose. Use as directed by clinicians.	0.1333
	1.0% cream	45 g tube	7.73		0.1718
	2.5% cream	45 g tube 225 g jar	9.06 45.32[b]		0.2014
	1.0% lotion	60 mL bottle	9.52		0.1587
	2.5% lotion	60 mL bottle	12.60		0.2100
	0.5% ointment	15 g tube 454 g jar	2.00 60.52[b]		0.1333
	1.0% ointment	15 g tube 454 g jar	0.58 17.71		0.0390
Hydrocortisone valerate (HydroVal)	0.2% cream	15 g tube 45 g tube 60 g tube	1.97 5.91 7.88	Small amount to affected area twice daily. Discontinue as soon as lesions heal or if no response.	0.1313
	0.2% ointment	15 g tube 60 g tube	1.97 7.88		0.1313
Mometasone furoate (generic)	0.1% cream	15 g tube 50 g tube	7.89 26.32	Thin film to affected areas twice daily.	0.5263
	0.1% lotion	30 mL bottle 75 mL bottle	10.07 25.18		0.3358
	0.1% ointment	15 g tube 50 g tube	3.38 11.26		0.2252
Triamcinolone acetonide (various)	0.1% cream	30 g tube	1.60	No recommended daily dose. Use as directed by clinicians.	0.0533

emol = emollient; PDE4 = phosphodiesterase type 4.

Table 8: CADTH Cost Comparison Table of Topical Calcineurin Inhibitors for Atopic Dermatitis

Drug/Comparator	Strength and Form	Package Size	Price per Package ($)	Recommended Dose	Price per Gram/mL ($)
Topical Calcineurin Inhibitors					
Pimecrolimus (Elidel)	1% cream	30 g tube 60 g tube	70.36 140.72	Thin layer to affected area twice daily, discontinue when resolved or after three weeks if no improvement or exacerbation.	2.3453
Tacrolimus (Protopic)	0.03% cream	30 g tube 60 g tube 100 g tube	67.83 135.66 226.10	Thin layer to affected area twice daily. Discontinue after six weeks if no improvement or exacerbation.	2.2610
	0.1% ointment	30 g tube 60 g tube 100 g tube	72.56 145.12 241.86		2.4186

Source: ODB Formulary list prices (July 2018)[15] unless otherwise indicated. Recommended doses from respective product monographs unless otherwise indicated.

Appendix 2: Additional Information

Table 15: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments Reviewer to provide comments if checking “no”	The manufacturer provided two additional models as part of a CADTH request for additional information given that the originally submitted model did not permit reporting of sequential probabilistic analysis results.[24] Of note, the model provided to CADTH on August 2nd was found to be highly unstable. The reason for the instability between the August 2nd version of the model, the original model, and the final model submitted to CADTH on August 20th remains unclear. No parameter inputs were found to have been changed. Furthermore, the justification for a patient-level simulation also remains unclear. The majority of the coding was within the Visual Basic for Applications codes, making the model less transparent to evaluate.		
Was the material included (content) sufficient?		X	
Comments Reviewer to provide comments if checking “poor”	Manufacturer provided clarification in the form of responding to the data on file request. Further clarifications were provided at the time of manufacturer’s comments.		
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking “poor”			

Table 16: Author Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☐ Adaptation of global model/Canadian model done by the manufacturer

☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify): Uncertain as not indicated in the submission from the manufacturer

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document			X
Authors had independent control of the methods and right to publish analysis			X

CDR = CADTH Common Drug Review.

Appendix 3: Summary of Other HTA Reviews of Drug

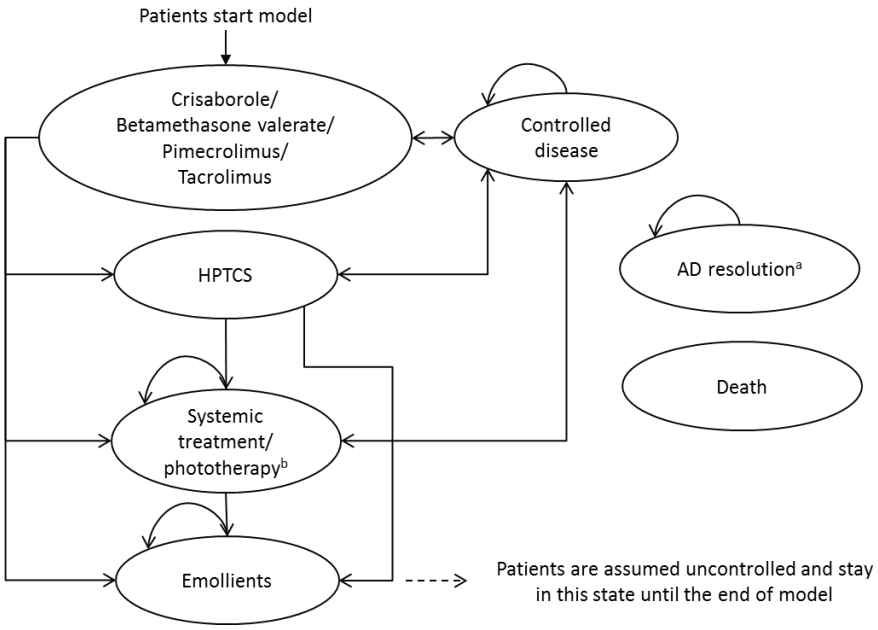
Crisaborole has not been reviewed by the National Institute for Health and Care Excellence (UK), the Scottish Medicines Consortium (Scotland), or the Pharmaceutical Benefits Advisory Committee (Australia) for the requested CADTH Common Drug Review indication. Crisaborole is currently undergoing review by Quebec's Institut national d'excellence en santé et en services sociaux, but the results are not publicly available.[25]

Appendix 4: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer submitted a microsimulation model that ran 10,000 individual patients through Markov health states and then averaged their costs and quality-adjusted life-years (QALYs) to estimate the expected outcomes for each treatment. Patients with mild-to-moderate atopic dermatitis (AD) entered the model initiating treatment on crisaborole or its comparators (i.e., betamethasone valerate, pimecrolimus, or tacrolimus). Treatment response in terms of disease control (i.e., Investigator's Static Global Assessment [ISGA] score of 0 to 1 at day 28 to 29) were assessed after the first month of treatment and, in patients with adequate disease control, patients would transition to the "controlled disease" state. Discontinuation of the initial treatment due to a lack of efficacy or adverse effects would result in switching to another line of therapy. The model assumed patients could not return to a prior line of therapy if they had prior history of failed treatment response and, if patients do not achieve response on their current treatment, specific rules to switching were followed (e.g., patients on high-potency topical corticosteroids [HPTCS] may switch to systemic therapy/phototherapy or emollients; patients on systemic therapy/phototherapy may only switch to emollients). Emollients were considered the last treatment choice and represented uncontrolled disease. The model structure is presented in Figure 1. In addition, the pediatric model further permitted children to have spontaneous AD resolution at any point in the model.[2]

Figure 1: Model Structure Diagram



AD = atopic dermatitis; HPTCS = high-potency topical corticosteroid.

[a] For children only.

[b] Dupilumab is also included in this treatment state.

Source: Manufacturer's pharmacoeconomic submission.[2]

Table 9: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	AD-301 and AD-302.[2,11,12]	Appropriate according to the clinical experts consulted for this review. However, subgroup analysis by severity may have proven useful given that the clinical review noted a relatively modest treatment effect (not statistically significant) in patients with mild disease at baseline, whereas treatment effect was statistically significant between groups in patients with moderate disease at baseline. According to the clinical expert consulted on this review, patients with mild AD are expected to have limited room for improvement compared with those with moderate disease. Given that patients with moderate disease are more likely to benefit from treatment, a different cost-effectiveness of crisaborole may be observed for different disease severities.
Efficacy	Crisaborole, pimecrolimus, and tacrolimus response was taken from the manufacturer's NMA.[4] RR of response for betamethasone valerate compared with pimecrolimus was estimated from a published systematic review that compared, at a class level, TCIs to TCS.[5]	Potential heterogeneity in the manufacturer's submitted NMA was identified with respect to baseline characteristics. As the manufacturer's NMA combined all patients regardless of age, there remains uncertainty to whether relative treatment effects differ by patient age which has not been fully explored in the manufacturer's economic model. It is unclear why the manufacturer's sponsored NMA did not identify any relevant studies on TCS. The relative efficacy of crisaborole compared with betamethasone valerate that was estimated in the manufacturer's model was considered to be highly uncertain as the approach taken to calculate relative efficacy was inappropriate. Incorporating the RR from the meta-analysis by Broeders et al. into the manufacturer's NMA implicitly assumes that both these studies were similar. The manufacturer's approach to combine the RR from one study to probabilities derived from an NMA does not adjust for potential heterogeneity that may exist between studies (e.g., baseline characteristics, length of therapy, dosing). Concerns were noted by CADTH as only one of the trials included in the meta-analysis by Broeders et al. was conducted in patients with mild-to-moderate AD (reflecting Health Canada's indication for crisaborole) with the remaining studies conducted in patients with more severe forms of AD.
Natural history	Various sources,[16-21,26,27] majority came from manufacturer's confidential data sources.[3]	Many of the assumptions made were considered inappropriate (Table 10). The severity of AD waxes and wanes whereas the clinical expert considered the progression of disease severity to not be reflective of clinical observation.
Utilities	Utilities were from published literature and reported separately for subgroups of adults and children.[6,7,13,14] EQ-5D (adults) HUI2 (children)	The majority of the utility weights for the adult population came from a utility study on adult patients with AD.[7] Utilities for the children subgroup were based on numerous unsubstantiated assumptions in order to map utility values to different disease severities. CADTH considered the assumptions to not be sufficiently justified. No AE-related disutilities were considered in the model.

Data Input	Description of Data Source	Comment
AEs (Indicate which specific AEs were considered in the model)	AEs resulting in treatment discontinuation were informed by published literature.	AEs were not associated with utilities impact. Rather, discontinuation due to AEs was assumed to lead to treatment switching and patient disease severity would be assigned according to the treatment switched to.
Mortality	Canadian life tables.[28] No treatment-specific mortality effects were included in the model.	Appropriate.
Health-state specific costs	Health-state costs were based on treatment received and patient disease severity.	Deemed appropriate by clinical experts.
Drug costs	Drug costs came from the ODB Formulary when possible or from a national database (IQVIA 2018).	Some drug prices had changed between the time the manufacturer undertook the analysis and when the analysis was assessed and needed to be updated.
Cost of managing AEs	The cost of a GP visit to manage AEs was taken from the Canadian Institute for Health Information, 2015 to 2016.[29]	Discontinuation due to AEs resulted in an office visit with a cost of $63.19.

AD = atopic dermatitis; AE = adverse event; DLQI = Dermatology Life Quality Index; EASI = Eczema Area And Severity Index; EQ-5D = EuroQol 5-Dimensions questionnaire; GP = general practitioner; HRQoL = health-related quality of life; HUI2 = Health Utilities Index Mark 2; NMA = network meta-analysis; ODB = Ontario Drug Benefit; RR = relative risk; TCI = topical calcineurin inhibitor; TCS = topical corticosteroids.

Table 10: Manufacturer's Key Assumptions

Assumption	Comment
28-day efficacy data from trial can be extrapolated for the duration of the treatment use.	No other assumptions were tested about the extrapolation of the treatment effect.
Patients could not switch to a comparator or to a treatment they had tried and failed previously.	Inappropriate. This does not match current practice where patients may retry treatments that have failed in the past. This assumption indirectly results in patients developing more severe AD over time and does not reflect the natural history of the disease in which the severity waxes and wanes.
Patients who fail crisaborole cannot try betamethasone or pimecrolimus or tacrolimus.	The clinical experts suggested that patients who have failed crisaborole would likely switch to betamethasone valerate.
Patient disease severity is assigned based on what treatment they receive.	Inappropriate. Disease severity mix was informed by the baseline characteristics of select trial. According to the clinical experts, disease severity would impact treatment choice rather than the contrary.
Patients transition every month.	In clinical practice it is unlikely that patients would be assessed less than every three months. This would accelerate the speed of switching treatments which would increase the costs of treatments and reduce utilities as patients go on to more expensive treatments and subsequent line of treatment resulted in patients being assigned to more severe AD.
The amount of TCS and TCIs used were assumed to be the same as crisaborole.[2]	Probably appropriate.
Utilization was assumed to be 45 g in children and 60 g in adults.	Inappropriate, although unlikely to impact model. According to the clinical expert consulted on this CDR, utilization is dependent on age due to differences in body surface area. Patients between the ages of 2 years to 5 years are expected to use one-fifth of an adult dose; patients between the ages of 5 years to 11 years would use between one-quarter to one-half of an adult dose, while those older than 12 years of age would have utilization similar to adults. However, if utilization is expected to be identical across treatment, this is probably an appropriate simplification.
No costs of emollients are included in the model.	This was justified since it was assumed that all patients would be on emollients. However, children whose AD resolves would not be on

Assumption	Comment
	emollients, therefore there may be a difference in emollient costs for treatments that are more likely to result in resolution. It is expected that the impact would be small, given the cost of emollients.

AD = atopic dermatitis; CDR = CADTH Common Drug Review; TCI = topical calcineurin inhibitor; TCS = topical corticosteroids.

Table 11: Severity by Treatment State

Treatment	Mild	Moderate	Severe	Source
Initial treatment (crisaborole, TCI, betamethasone valerate)	38.5%	61.5%	NA	Paller, 2016[16]
HPTCS	0%	[redacted]	[redacted]	Hanifin, 2001;[18] Paller, 2001;[17] Ellis, 2003[27]
Phototherapy	15.8%	60.5%	23.7%	Rose, 2014[19]
Systemic therapy	0%	20.0%	80.0%	Goujon, 2017[20]
Dupilumab	NA	50.0%	50.0%	Simpson, 2016[21]

HPTCS = high-potency topical corticosteroids; NA = not available; TCI = topical calcineurin inhibitor.

Source: Manufacturer's pharmacoeconomic submission.[2]

Manufacturer's Results

Table 12: Detailed Deterministic Results of the Manufacturer's Base Case — Primary Analysis

	Crisaborole (a)	Pimecrolimus (b)	Betamethasone Valerate (c)	Difference (a–b)	Difference (a–c)
Children Subgroup					
QALYs	10.89[a]	10.87[a]	10.85[a]	0.02	0.04
Cost ($)					
Drug acquisition costs	193	173	6	20[b]	187[b]
Other medical costs	2,548	2,572	2,588	–24[b]	–40[b]
Adverse event costs	1	1	1	0[b]	0[b]
Total costs	2,743	2,746	2,596	–3	147
ICUR ($/QALY)				Dominant	3,956
Adult Subgroup					
QALYs	0.81	0.81	0.81	0.002	0.004
Cost ($)					
Drug acquisition costs	239	220	8	19[b]	231[b]
Other medical costs	523	554	571	–31[b]	–48[b]
Adverse event costs	1	1	1	0[b]	0[b]
Total costs	763	775	581	–12	182
ICUR ($/QALY)				Dominant	44,110

ICUR= incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] Corrected. The manufacturer's pharmacoeconomic report appears to have presented life-years gained.

[b] Calculated.

Source: Manufacturer's pharmacoeconomic submission.[2]

Table 13: Detailed Deterministic Results of the Manufacturer's Base Case — Secondary Analysis

	Crisaborole (a)	Pimecrolimus (b)	Tacrolimus (c)	Difference (a–b)	Difference (a–c)
Children Subgroup					
QALYs	10.91	10.88	10.90	0.02	0.01
Cost ($)					
Drug acquisition costs	193	173	178	20[a]	15[a]
Other medical costs	2,550	2,574	2,559	–24[a]	–9[a]
Adverse event costs	1	1	1	0[a]	0[a]
Total costs	2,745	2,748	2,738	–3	7
ICUR ($/QALY)				Dominant	721
Adult Subgroup					
QALYs	0.81	0.81	0.81	0.002	–0.001
Cost ($)					
Drug acquisition costs	243	225	255	18	–12
Other medical costs	513	544	507	–31	6
Adverse event costs	1	1	2	0	–1
Total costs	757	770	763	–13	–6
ICUR ($/QALY)				Dominant	12,435[b]

ICUR= incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] Calculated.

[b] Tacrolimus is the cost-effective option at a cost-effectiveness threshold greater than $12,435 per additional QALY.

Source: Manufacturer's pharmacoeconomic submission.[2]

Additional CADTH Common Drug Review Reanalyses

Table 14: CADTH Reanalysis of Limitations Incorporating Betamethasone According to Manufacturer's Approach — Primary Analysis

	Scenario	Treatments	QALYs	Cost	ICUR (per QALY)
	Base Case for Children, Submitted by Manufacturer	Betamethasone valerate	10.85	$2,596	–
		Crisaborole	10.89	$2,743	$3,956
		Pimecrolimus	10.87	$2,746	Dominated
1.1[a]	Updated costs	Betamethasone valerate	10.773	$2,608	–
		Pimecrolimus	10.803	$2,757	$4,892
		Crisaborole	10.787	$2,762	Dominated
2.1[a]	Adult utilities	Betamethasone valerate	11.757	$2,614	–
		Crisaborole	11.772	$2,765	$10,393
		Pimecrolimus	11.765	$2,771	Dominated
3.1[a]	No progression	Betamethasone valerate	11.330	$2,243	–
		Crisaborole	11.350	$2,398	$7,879
		Pimecrolimus	11.340	$2,403	Dominated
4.1[b]	CDR reanalysis	Betamethasone valerate	12.089	$1,983	–
		Crisaborole	12.094	$2,143	$35,108

	Scenario	Treatments	QALYs	Cost	ICUR (per QALY)
		Pimecrolimus	12.091	$2,143	Dominated
	Base Case for Adults, Submitted by Manufacturer	Betamethasone valerate	0.81	$581	–
		Crisaborole	0.81	$763	$44,110
		Pimecrolimus	0.81	$775	Dominated
1.1[a]	Updated costs	Betamethasone valerate	0.808	$568	–
		Crisaborole	0.811	$753	$48,339
		Pimecrolimus	0.809	$765	Dominated
2.1[ab]	Lifetime horizon	Betamethasone valerate	31.792	$13,205	–
		Pimecrolimus	31.796	$13,429	ED
		Crisaborole	31.801	$13,434	$25,761
3.1[a]	No progression	Betamethasone valerate	0.817	$530	–
		Crisaborole	0.820	$720	$81,906
		Pimecrolimus	0.819	$731	Dominated
4.1[b]	CDR reanalysis	Betamethasone valerate	32.811	$11,428	–
		Pimecrolimus	32.814	$11,658	ED
		Crisaborole	32.817	$11,662	$40,072

CDR = CADTH Common Drug Review; ED = extendedly dominated; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] Indicates those scenarios included in the CDR base-case reanalysis.

[b] Deterministic analysis run due to length of time to run analysis (approximately 14 hours).

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