

CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

DUPIUMAB (DUIXENT)

(Sanofi Genzyme, a division of sanofi-aventis Canada Inc.)

Indication: Indicated for the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

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Abbreviations

AD	atopic dermatitis
DUP	dupilumab
EASI	Eczema Area and Severity Index
EASI-50	Eczema Area and Severity Index score improvement from baseline $\geq 50\%$
EASI-75	Eczema Area and Severity Index score improvement from baseline $\geq 75\%$
ICER	incremental cost-effectiveness ratio
EQ-5D	EuroQol 5-Dimensions
SOC	standard of care
QALY	quality-adjusted life-year

Executive Summary

The executive summary comprises two tables (Table 1: Submitted for Review and Table 2: Summary of Economic Evaluation) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Dupilumab (Dupixent), 200 mg or 300 mg single-use syringe with a needle shield or pre-filled syringes in packs of 1 or 2
Submitted price	Dupilumab, 200 mg, subcutaneous injection: \$959.94 per pack of 1 Dupilumab, 300 mg, subcutaneous injection: \$959.94 per pack of 1
Indication	For the treatment of patients aged ≥ 12 years with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	25-09-2019
Reimbursement request	Patients aged ≥ 12 years with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies, or when those therapies are not advisable, and/or who are refractory to or ineligible for systemic immunosuppressant therapies (i.e., due to contraindications, intolerance, or need for long-term treatment)
Sponsor	Sanofi Genzyme, a division of sanofi-aventis Canada Inc.
Submission history	Previously reviewed: Yes Indication: Adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable Recommendation date: June 27, 2018 Recommendation: Do not reimburse

AD = atopic dermatitis; NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis
Target population	Patients aged ≥ 12 years with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies, or when those therapies are not advisable ^a
Treatment	DUP +SOC (topical therapy ^b)
Comparator	SOC
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (86 years)
Key data sources	AD-1526, SOLO 1, SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD CAFÉ trials
Submitted results for base-case and key scenario analyses	<p>Base case: patients whose disease is not adequately controlled with topical prescription therapies, or for whom those therapies are not advisable</p> <ul style="list-style-type: none"> ICER = \$50,133 per QALY (incremental cost = \$127,607; incremental QALYs = 2.55) <p>Key scenario analysis:</p> <ul style="list-style-type: none"> Patients who could no longer use systemic immunosuppressant therapies (reimbursement-request population: ICER = \$52,168 per QALY)
Key limitations	<ul style="list-style-type: none"> Relevant comparators, such as immunosuppressants (e.g., methotrexate and cyclosporine), are prescribed to treat moderate-to-severe AD but are not included as comparators in the model. The sponsor assumed data from clinically different patient populations could be combined to follow patients throughout the model. CADTH did not consider this application of data to be appropriate. The clinical data indicate that DUP's efficacy differs based on disease severity; this impact could not be assessed by CADTH given differences between the available clinical data and outcomes assessed in the model. Exploratory analyses highlighted that duration of benefit between weeks 16 and 52 appeared to be a more important driver of the results than treatment response at week 16. The sponsor incorporated treatment-specific utility values, which do not reflect best practices. Further, the methodology used to derive these values was associated with substantial uncertainty. The utility estimates lacked face validity in several respects: the baseline utility score was notably lower than those reported in other HTA appraisals, the utility weight for DUP + SOC responders was higher than Canada's EQ-5D population norm, and data from distinctly different populations were used, which resulted in an implausible age-related decrease in utility between ages 18 and 19. The inclusion of caregiver disutilities in the base case does not align with the public payer perspective methodology. The durability of treatment response beyond the trial duration remains uncertain; however the incremental benefit of DUP + SOC compared with SOC appeared to be overestimated. The sponsor incorporated expert-elicited frequencies of resource use that do not align with Canadian clinical practice based on feedback from the clinical expert consulted by CADTH for this review.
CADTH reanalysis results	<ul style="list-style-type: none"> The CADTH reanalysis included the exclusion of caregiver utilities; alternate measures for treatment response, utility, durability of response; and a macro-level costing approach. CADTH identified other limitations that could not be assessed in reanalyses. ICER: \$136,025 per additional QALY gained (1.26 incremental QALYs, \$171,694 incremental costs).

Component	Description
	<ul style="list-style-type: none"> • The results in the indicated population warrant careful interpretation as 95% of DUP + SOC's incremental benefit was accrued during time points beyond which clinical data are available. • A price reduction of 54% was required for DUP + SOC to achieve an ICER below \$50,000 per QALY gained. • CADTH undertook a scenario analysis in the reimbursement-request population,^a which resulted in a similar ICER (\$133,877 per QALY gained).

AD = atopic dermatitis; DUP = dupilumab; EQ-5D = EuroQol 5-Dimensions; HTA = health technology assessment; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care.

^a A secondary study objective was to assess the cost-effectiveness of DUP + SOC versus SOC in patients aged 12 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable and/or who are refractory to or ineligible for systemic immunosuppressant therapies.

^b The sponsor did not indicate which topical therapies were included in the standard of care treatment for moderate-to-severe AD.

Conclusions

CADTH undertook reanalyses to address limitations relating to the application of treatment effects, utility estimates, resource use, and long-term durability of treatment effects.

Following reanalysis of the Health Canada–indicated and reimbursement-request populations, CADTH estimated the corresponding incremental cost-effective ratios for dupilumab (DUP) plus SOC versus SOC alone to be \$136,025 per additional quality-adjusted life-year (QALY) gained and \$133,877 per QALY gained for the Health Canada–indicated population. A reduction of 54% in DUP's price was required to improve its cost-effectiveness, relative to SOC, in both populations and generate an incremental cost-effectiveness ratio of less than \$50,000 per QALY. The results for the reimbursement request population were similar.

The results of the CADTH reanalysis remain uncertain as multiple limitations could not be addressed. CADTH was unable to assess the cost-effectiveness of DUP + SOC compared to alternative comparators that are presently used by patients with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies; nor was it possible to determine how DUP's cost-effectiveness differed in patients with moderate AD versus those with severe AD. Additional scenario and exploratory analyses were undertaken that highlighted the uncertainty associated with the assumptions for durability of effect for DUP + SOC and SOC alone.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups that participated in the CADTH review process as the information pertains to the economic submission.

Two patient groups contributed to the CADTH appraisal of the sponsor's pharmacoeconomic analysis of dupilumab.¹

The patients expressed a desire for flare prevention and the elimination of AD-related symptoms (e.g., itching, burning, pain, open sores, sleep disturbance, anxiety and depression) as the overarching goals of treatment. The development of such outcomes may reduce the condition's impacts on quality of life that the patients noted: itching, pain, loss of productivity, social isolation, interrupted sleep, mood changes, poor self-esteem, loss of energy, increased stress, and suicidal thoughts. Among adolescents, the three primary issues were avoidance of social activities, inability to participate in sports and physical activities, and interrupted sleep. Patients who were treated with dupilumab (DUP) reported improvements in their disease symptoms and quality of life. The sponsor modelled the costs associated with incident skin infections, which likely encompassed some of the AD-related symptoms identified by patients.

The sponsor accounted for caregiver utility and productivity loss in its scenario analyses, but did not explore other key considerations identified by patients (e.g., out-of-pocket expenses for mental health services and transportation costs).

Economic Review

The current review is for DUP (Dupixent) plus SOC; i.e., unspecified topical therapy) compared to SOC alone for patients aged ≥ 12 years with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies, or when those therapies are not advisable.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis of DUP plus SOC (DUP + SOC) versus SOC.¹ The model population comprised patients aged 12 years or older with moderate-to-severe AD for whom topical prescription therapies failed to achieve effective disease control or were not advisable. This population was consistent with the Health Canada–indicated population. However, the sponsor's reimbursement request also included patients who are refractory to, or ineligible for, systemic immunosuppressant therapies due to contraindications, intolerance, or a need for long-term treatment.² To address these patients, the sponsor conducted analyses in subgroups of those who could no longer take systemic immunosuppressant therapies (e.g., methotrexate and cyclosporine) with additional age criteria. The trial of DUP in adolescents (AD-1526) assessed patients with moderate-to-severe AD who had demonstrated a recent history of inadequate response to topical therapies or for whom topicals were not advised (due to intolerance, side effects, or safety risks) and excluded patients who had been treated with immunosuppressants, immunomodulators, or phototherapy within four weeks of baseline. This exclusion criterion may have better reflected the reimbursement request compared with the trials of DUP in

adults (SOLO 1, SOLO 2, LIBERTY AD CHRONOS, and LIBERTY AD CAFÉ), which did not have the same clause regarding immunosuppressant therapies.³⁻⁷

The recommended dose of dupilumab is age- and weight-specific. In adolescents 12 to 17 years old who weigh < 60 kg, two subcutaneous injections of 200 mg of DUP should be administered as the loading dose during the first week, after which one 200 mg injection should be taken every other week.⁸ In adolescents who weigh ≥ 60 kg, and in all adults (≥ 18 years), the recommended loading dose is 600 mg of DUP (two 300 mg injections), followed by 300 mg every other week. At the submitted price of \$959.94 for each of the 200 mg and 300 mg injections, the first-year cost of DUP is \$25,918 per patient and the annual maintenance cost is \$24,958 per patient. In the model, the sponsor assumed DUP treatment dosage was 200 mg (for adolescents < 60 kg) or 300 mg (for adolescents ≥ 60 kg and adults) every two weeks.¹ No cost was associated with the use of topical therapy in the model.

The clinical outcomes of interest were QALYs and life-years. The economic analysis was undertaken over a lifetime time horizon (86 years) from the perspective of the public health care payer. A discount of 1.5% per annum was applied to both costs and outcomes.

Model Structure

The model structure included a short-term (one-year) phase for the 16- and 52-week assessments (based on the AD-1526, SOLO 1, SOLO 2, LIBERTY AD CHRONOS, and LIBERTY AD CAFÉ trials), and a lifetime model for the maintenance phase.^{1,3-6} The short-term phase was based on a decision tree (Figure 1) that modelled all patients as nonresponders until the first treatment response assessment of whether the Eczema and Severity Score Index (EASI) scores improved by ≥ 50% compared with baseline (EASI-50). The sponsor modelled week-16 efficacy outcomes from the AD-1526 trial at week 8 based on cumulative-time-to-response plots that suggested most patients who responded did so before 8 weeks.^{1,9} In the DUP arm, patients who responded to treatment stayed on DUP until 52 weeks, at which point patient responses were assessed according to data from the LIBERTY AD CHRONOS trial. All nonresponders were treated with SOC. If patients were deemed responders at weeks 16 and 52, they entered the response state for the respective treatment in a Markov state-transition model (Figure 2) of the maintenance phase. The Markov model incorporated a one-year cycle time to which a half-cycle correction was applied, and consisted of four health states: DUP + SOC treatment with response, SOC treatment with response, SOC treatment without response, and death. In the maintenance phase, patients were allowed to discontinue DUP and transition to either SOC treatment state. Patients in the SOC with response state could transition to the SOC without response state. Patients could transition from each of these states to an absorbing death state.

Model Inputs

In the base case, the patients' baseline characteristics reflected the AD-1526 trial's distribution of risk factors in adolescent patients.⁹ Patients entered the model at 14 years of age; 59% were male and 51% had a weight of < 60 kg (each received 200 mg injections of DUP until age 18, followed by 300 mg injections thereafter). The sponsor assumed that all patients independently administered the injections and were 100% compliant to treatment.

The clinical efficacy of DUP + SOC and SOC were obtained from the AD-1526 and LIBERTY AD CHRONOS trials.^{4,9} Response at 16 weeks was based on Study 1526 for both DUP + SOC (61.0%) and SOC (12.9%).⁹ For DUP + SOC, a conditional probability of sustaining the response for 52 weeks was modelled based on the sponsor-reported proportions of those who achieved a 16-week response and responders at week 52 from the CHRONOS study [REDACTED].³ Similarly, for SOC, the conditional probability was calculated for all SOC-treated patients given the proportions of responders at week 16 and

at week 52 from CHRONOS [REDACTED].³ Maintenance of treatment effect beyond 52 weeks was based on clinical-expert feedback that suggested the probability of sustaining treatment response over time was much higher for DUP + SOC (98% in year 2 to 92% in year 5 and beyond) than for SOC (37% in year 2 to 0% in year 4 and beyond). A discontinuation rate of 6.3% per annum was derived from the SOLO trials.¹⁰

The sponsor assumed that treatment did not affect mortality risk. Age- and sex-specific death rates, from the National Life Tables for Canada, were weighted by the cohort's proportion of males and females and modelled annually.¹¹

Health-state utility values were collected (at weeks 1, 2, 4, 6, 8, 12, 16, 20, 24, and 28) in the SOLO trials using EuroQol 5-Dimensions (EQ-5D) 3-Levels questionnaire values.^{5,6} Data from a subgroup of patients in the SOLO trial aged 18 to 25 were used as a proxy for adolescent patients (aged 14 to 18 years) and stratified according to treatment and whether patients were responders (i.e., DUP + SOC = [REDACTED]; SOC = [REDACTED]) or not (i.e., DUP + SOC = [REDACTED]; SOC = [REDACTED]). Covariates were identified and regression coefficients were applied to the baseline treatment-specific values based predominantly on observed data from the 1526 trial (except for the baseline EQ-5D utility score). When patients turned 19 years of age, data from the full SOLO trial were modelled by treatment and response status (responders: DUP + SOC = [REDACTED], SOC = [REDACTED]; nonresponders: DUP + SOC = [REDACTED], SOC = [REDACTED]). The model allowed for the use of results based on a regression of the adult population data. Caregiver-related utility gains for responders were incorporated as part of the base case, while impact on quality of life due to adverse events was not modelled.¹

The model included acquisition costs of DUP, health-state medical costs (by responder status), and the cost of treating adverse events. Drug costs for DUP were based on the sponsor's submitted price at the dose regimen identified in the product monograph. Costs for all scheduled doses were incurred in accordance with an assumption of 100% treatment compliance, although a rationale or source for this approach was not provided. The sponsor excluded the cost of self-injection training with a nurse for one hour on the assumption that their planned patient-support program would provide such resources. The drugs that comprised SOC (types of topical therapies were not identified) were not costed to avoid issues of double-counting, as health state-specific costs were present in the model based on responder status. Nonresponders incurred a greater number of medical visits (e.g., to see a dermatologist and receive primary care) compared with responders. The frequency of resource use that the nonresponders and responders incurred reflected the opinions of clinical experts. Lastly, the sponsor modelled the cost of a dermatologist visit to treat a one-time injection-site reaction among DUP users, as well as for the treatment of adverse events each cycle. Patients taking either intervention were at risk of developing allergic conjunctivitis, infectious conjunctivitis, oral herpes, or a skin infection. All cost estimates were sourced from the Ontario Drug Formulary, Ontario Schedule of Benefits, Ontario Case Costing Initiative, and the Ontario Schedule of Benefits for Laboratory Services.¹²⁻¹⁴

Summary of Sponsor's Economic Evaluation Results

All analyses were run probabilistically (5,000 iterations for the base case and scenario analyses). The results were similar between the probabilistic and deterministic analyses. The probabilistic findings are presented below.

Base-Case Results

The sponsor's base case comprised of the Health Canada-indicated population. In these results, DUP + SOC was associated with an additional \$127,607 and 2.55 QALYs compared with SOC over the 86-year time horizon (Table 3). This resulted in an incremental cost-effectiveness ratio (ICER) of \$50,133 per QALY gained for DUP + SOC compared to SOC.

The results were primarily driven by drug acquisition costs, which were partially offset by savings in medical costs (Table 12). The majority (96%) of the incremental QALYs for DUP + SOC were accrued during the extrapolation period (i.e., after 52 weeks of observed trial data). The sponsor’s base case was associated with a notable degree of decision uncertainty as DUP + SOC had a 49% chance of being the optimal intervention at a willingness-to-pay threshold of \$50,000 per QALY.

To address the reimbursement request, the sponsor also estimated the cost-effectiveness of DUP in a subgroup of patients who were refractory to, or ineligible for, systemic immunosuppressant therapies. The ICER for DUP + SOC versus SOC was \$52,168 per QALY gained (Table 13).

Table 3: Summary of the Sponsor’s Economic Evaluation Results

	Total costs (\$)	Incremental cost of DUP + SOC (\$)	Total QALYs	Incremental QALYs of DUP + SOC (\$)	ICER (\$ per QALY)
SOC	358,555	Reference	23.67	Reference	Reference
DUP + SOC	486,163	127,607	26.22	2.55	\$50,133

DUP = dupilumab; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care.

Source: Sponsor’s pharmacoeconomic submission.¹

Note: The submitted results were based on the publicly available prices of the comparator treatments. Total expected life-years (43.04 years) were derived from the deterministic analysis, but likely do not differ between comparators given that the total expected QALYs estimated in the probabilistic analysis were similar (DUP + SOC = 26.22; SOC = 23.67).

Sensitivity and Scenario Analysis Results

The sponsor assessed several model features in probabilistic scenario analyses, as reported in Table 13. Three scenarios suggested a > 10% increase in the ICER. When the model population included the SOLO trial’s subgroup of adults whose mean age was 34 years, the ICER was \$7,286 greater than the base-case estimate (scenario 11: \$57,419 per QALY gained). The addition of patients who could no longer use systemic immunosuppressant therapies to this subgroup in another scenario produced a similar ICER (scenario 12: \$57,991 per QALY). The greatest increase from the base-case estimate occurred when utility values were based on the sponsor’s unpublished study of EQ-5D data among children with AD. When the analysis undertook a societal perspective, the ICER decreased by approximately 30%.

CADTH Appraisal of the Sponsor’s Economic Evaluation

CADTH identified several key limitations to the sponsor’s analysis that have notable implications for the economic analysis:

- **Omission of relevant comparators:** In the Health Canada–indicated population, the current SOC for the treatment of AD in adolescents and adults includes the use of systemic immunosuppressants, such as methotrexate and cyclosporine. The benefits and costs of these widely used treatments were not included in the model. Systemic immunosuppressants are less expensive than DUP and more effective than SOC. The exclusion of relevant comparators from the analysis limits the assessment of the relative value of DUP + SOC in the Health Canada–indicated population. This limitation does not apply to the analysis for the reimbursement-request population, which included individuals who are refractory to or ineligible for systemic immunosuppressant therapies, for which SOC (i.e., topical therapy) is the only relevant comparator.

- Given the lack of comparative clinical effectiveness data presented by the sponsor and the structure of the submitted economic model, CADTH was unable to conduct a reanalysis to assess this limitation.
- **The adolescent trial population was clinically different from the adult trial populations:** The sponsor used data from the AD-1526 trial to define the population's baseline characteristics and treatment response at week 16. Study AD-1526 consisted of adolescents who had more severe AD than those in the studies of DUP in adults (see CADTH Clinical Report).^{5,6,9} Furthermore, in AD-1526, topical prescription therapies, and systemic immunosuppressants were reserved for use as rescue medication, even among members of the placebo group who otherwise applied only moisturizers throughout follow-up. In the adult studies, patients on DUP concomitantly used emollients (SOLO 1⁵ and SOLO 2⁶) or a medium-potency topical corticosteroid (LIBERTY AD CHRONOS⁴ and LIBERTY AD CAFÉ³). As such, the use of AD-1526 data may better represent the sponsor's reimbursement-request population. The combination of these data sources may limit the generalizability of the sponsor's results to the indicated population given the inherent differences in the disease status of the population. Further implications of the differences in the patient populations are highlighted in a subsequent discussion of limitations.
 - CADTH considered alternate scenarios in which different efficacy assumptions were applied for the different populations.
- **The model lacked flexibility to assess relevant subgroups:** The trial data suggest that treatment effects differed depending on disease severity at baseline (see CADTH Clinical Report). This variation in effect was seen across the SOLO 1, SOLO 2, LIBERTY AD CHRONOS, and AD-1526 trials for both EASI scores improved by $\geq 75\%$ compared with baseline (EASI-75) and Investigator's Global Assessment outcomes, although the direction was not consistent across trials. These differences suggested the need to account for heterogeneity in DUP's efficacy outcomes through a subgroup analysis of DUP + SOC's cost-effectiveness based on disease severity. Separate assessments of individuals with moderate AD and those with severe AD could not be undertaken with the available clinical information. Consequently, the cost-effectiveness of DUP + SOC in such subgroups remains unknown.
 - CADTH was unable to explore how the cost-effectiveness of DUP + SOC may differ in patients with moderate AD versus those with severe AD given the available information for the outcome of interest. CADTH conducted exploratory analyses to present estimates for an alternate outcome (EASI-75). The consistency in the results for the moderate and severe populations, despite the differences in treatment response at week 16 between the groups, suggests that the duration of effect between weeks 16 and 52 has a larger impact on the results. This finding introduces some additional uncertainty to the results.
- **Treatment-specific utility values were associated with methodological uncertainty:** Under current guidelines for the conduct of economic evaluations, utilities should reflect the health states within the model and should not be specific to treatment.¹⁵ No justification was provided to support the use of the treatment-specific utility values, which were derived using preference weights for the British population to obtain EQ-5D 3-Level outcomes. A mixed-model regression analysis of data from a subgroup of patients in the SOLO trial aged 18 to 25 were used as a proxy for adolescent patients. The utility estimate for responders to DUP + SOC was also higher than the utility weight associated with response to SOC [REDACTED], a finding that the clinical expert consulted by CADTH did not consider to be reasonable. The methodology was associated with substantial uncertainty and introduced considerable bias in the estimated cost-effectiveness measures.

- CADTH used the utility weights estimated for patients on SOC in the SOLO trials to model the same utility weights for response and non-response in all patients, irrespective of treatment.^{4,5}
- **Utility estimates lacked face validity:** CADTH identified three issues in the modelled utility estimates' face validity. First, the baseline utility value [REDACTED] was lower than values previously reported for patients with moderate-to-severe AD by health technology assessment agencies (range: 0.64 to 0.70)¹⁶⁻¹⁸ and was based on a proxy population (18- to 25-year-olds from the SOLO trials).^{4,5} Second, the use of data from the two different sources (a proxy population to inform the utility values for adolescents aged 14 to 18 years and the full SOLO population for adults aged 19 years and older) resulted in an unrealistic decrease in utility [REDACTED] for patients once they turned 19 years of age. Third, the utility weight assigned to patients with response on DUP + SOC [REDACTED] was higher than the EQ-5D population norm among 18- to 24-year-olds in Canada (mean = 0.88; SD = 0.10), and did not appear to appropriately consider the differences in severity of disease at baseline between the adolescent and adult trial populations.^{9,19} The impact of using these estimates in the model likely overestimated DUP + SOC's total expected QALYs.
 - CADTH revised the baseline utility score and utility weights for treatment response. Alternative values, which were considered more appropriate, were sourced from the LIBERTY AD CHRONOS and SOLO trials, respectively.^{4,6}
- **Inclusion of caregiver disutilities in base case:** The sponsor included caregiver disutilities in the base case despite indicating that they adopted the public payer perspective. Per CADTH economic evaluation guidelines, such consequences are relevant to a societal, rather than a public payer, perspective, and should not have been considered in the base case.¹⁵ The inclusion of caregiver disutilities in the base case overestimated the total expected QALYs for DUP + SOC and underestimated the ICER for DUP + SOC versus SOC.
 - CADTH removed caregiver disutilities from the base case.
- **Use of incorrect 52-week treatment outcomes from the LIBERTY AD CHRONOS trial:** The CADTH clinical reviewers were unable to validate the efficacy measures that the sponsor reported were from the LIBERTY AD CHRONOS trial and were used to model treatment response outcomes at 52 weeks for both comparators. The use of data that could not be validated incorporated bias in the total QALYs estimated for each comparator.
 - CADTH revised these estimates based on the data reported in LIBERTY AD CHRONOS trial.
- **Durability of response beyond trial duration:** The model included treatment-specific assumptions to incorporate the durability of treatment response. Based on expert opinion, the sponsor assumed utility gains in DUP + SOC responders were stable over time, but that short-term gains in utility among the SOC responders diminished rapidly such that, by year 4, all SOC responders returned to their baseline utility values, adjusted by age. The clinical expert consulted by CADTH advised that patients on SOC would not revert to the baseline utility by year 4. The expert also noted that responders to DUP + SOC will be less likely to continue topical therapy than responders to SOC, which may result in fewer patients maintaining treatment efficacy than was captured by the submitted model. Such treatment-specific assumptions appear to underestimate the absolute benefit of SOC and may overestimate that of DUP + SOC. Other health technology assessment agencies considered alternate assumptions regarding the duration of effect, which suggested a longer maintenance of benefit for patients receiving SOC.²⁰
 - Given the expert's view that it is unlikely that SOC responders would lose all treatment benefits after year one, CADTH incorporated alternative waning assumptions for the SOC comparator based on the annual rate of rescue therapy or loss to follow-up in the

LIBERTY AD CHRONOS trial.⁴ Alternative assumptions were also tested in scenario analyses.¹⁶

- **Resource use and costs did not reflect clinical practice in Canada:** The sponsor adopted a micro-level costing approach to model costs by treatment and response status based on expert-elicited frequencies of resource use. However, some treatment-specific frequencies did not align with Canadian clinical practice according to the clinical expert consulted by CADTH. For example, SOC responders incurred three visits to the dermatologist each year, whereas DUP + SOC responders incurred one. In Canada, patients who develop the same response to interventions for AD would likely incur the same health care costs irrespective of treatment type. Furthermore, this approach did not account for cost and resource use for patients who develop less than the expected level of response to treatment, such as additional follow-up assessments. The incorporation of expert-elicited frequencies of resource use appear to underestimate the total expected cost of DUP + SOC.
 - CADTH used annual health care costs incurred by patients with AD, by response status, obtained from published data.^{21,22}
- **Treatment response definition based on marginal response:** The sponsor’s definition of treatment response was based on achieving EASI-50, which represents the clinical outcome for defining relative treatment response (rather than complete response). The clinical expert consulted by CADTH for this review notes that, in Canada, the most common clinical outcome that dermatologists use to assess AD-related treatment response is EASI-75 after 16 weeks, but that in practice, patients who experienced an EASI improvement of 40% or greater would likely be continued on treatment for at least an additional six months.
 - CADTH implemented a scenario analysis in which treatment response was based on the EASI-75 sourced from the pooled SOLO trial data.²³

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (See Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation

Sponsor’s key assumption	CADTH comment
Treatment with dupilumab included concomitant topical therapy.	Reasonable as dupilumab can be used with or without topical corticosteroids.
Efficacy (modelled as change in EASI score and utility weights) was assumed to occur at 8 weeks (halfway through the clinical assessment of 16 weeks).	The CADTH clinical expert noted that patients taking dupilumab are likely to develop AD-related changes soon after treatment onset.
No utility impacts associated with adverse events.	Reasonable as captured through treatment-related quality of life measures obtained throughout the dupilumab trials.

AD = atopic dermatitis; EASI = Eczema Area and Severity Index.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

CADTH undertook reanalyses that addressed limitations within the model, as summarized in Table 5. CADTH could not fully address limitations associated with the lack of relevant comparators and treatment compliance.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to the sponsor's base case		
None		
Changes to derive the CADTH base case		
1. Model population had limited generalizability to the indicated population	AD-1526 trial outcome data: <ul style="list-style-type: none"> 61.0% patients on DUP + SOC achieved EASI-50 at week 16 12.9% patients on SOC achieved EASI-50 at week 16 	Pooled SOLO trial outcome data: ²³ <ul style="list-style-type: none"> 67.0% patients on DUP + SOC achieved EASI-50 at week 16 23.3% patients on SOC achieved EASI-50 at week 16
2. Utility estimates lacked face validity	Baseline utility in all patients = █████	Baseline utility in all patients = 0.64
3. Treatment-specific utility values derived through regression of proxy data	Utility weights for treatment outcomes in patients were based on the SOLO 18- to 25-year-old subgroup. The values for patients on DUP + SOC: <ul style="list-style-type: none"> response = █████ non-response = █████ Values for patients on SOC: <ul style="list-style-type: none"> response = █████ non-response = █████ 	Utility weights for treatment outcomes in patients on were based on the SOLO full population dataset. <ul style="list-style-type: none"> DUP + SOC was then assumed to be equal to SOC alone (final value in model changes depending on other model assumptions)
4. Inclusion of caregiver utilities in the base case	Caregiver utility weight associated with: <ul style="list-style-type: none"> mild AD = █████ moderate-to-severe AD = █████ 	Removed caregiver utilities
5. Use of incorrect 52-week treatment response outcomes from the LIBERTY AD CHRONOS trial	EASI-50 response at week 52: <ul style="list-style-type: none"> █████% patients on DUP + SOC █████% patients on SOC 	EASI-50 response at week 52: <ul style="list-style-type: none"> 97.2% patients on DUP + SOC 81.4% patients on SOC
6. Durability of response beyond trial duration – for SOC	Proportion who sustained treatment benefits among patients on SOC: <ul style="list-style-type: none"> year 2 = 37% year 3 = 9% year 4 = 0% year 5+ = 0% 	Proportion who sustained treatment benefits among patients on SOC: <ul style="list-style-type: none"> year 2 = 43% year 3 = 18% year 4 = 8% year 5+ = 3%
7. Resource use and costs did not reflect clinical practice in Canada	Expert-elicited estimates of health care resource use	Annual cost estimates by response status: <ul style="list-style-type: none"> \$173.19 for all responders \$4,193.49 for all nonresponders
CADTH base case	Combine revisions (1 + 2 + 3 + 4 + 5 + 6 + 7)	

DUP = dupilumab; EASI-50 = Eczema Area and Severity Index score improvement from baseline \geq 50%; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years; SOC = standard of care.

CADTH undertook a stepped analysis, incorporating each change proposed in Table 5 to the sponsor's base case to highlight the impact of each change in Table 6.

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug	Total costs (\$)	Total QALYs	ICER (\$/QALYs)
Sponsor's base case	SOC ^a	358,555	23.67	—
	DUP + SOC	486,163	26.22	50,133
CADTH reanalysis 1	SOC ^a	357,297	23.07	—
	DUP + SOC	497,783	26.49	50,363
CADTH reanalysis 2	SOC ^a	359,409	25.63	—
	DUP + SOC	486,395	27.96	54,704
CADTH reanalysis 3	SOC ^a	357,867	23.63	—
	DUP + SOC	485,668	25.58	65,371
CADTH reanalysis 4	SOC ^a	359,340	23.66	—
	DUP + SOC	485,524	25.61	64,683
CADTH reanalysis 5	SOC ^a	359,408	23.68	—
	DUP + SOC	491,612	26.33	49,861
CADTH reanalysis 6	SOC ^a	358,398	23.67	—
	DUP + SOC	485,990	26.21	50,260
CADTH reanalysis 7	SOC ^a	181,966	23.67	—
	DUP + SOC	332,951	26.22	59,167

DUP = dupilumab; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years; SOC = standard of care.

Note: The submitted results were based on the publicly available prices of the comparator treatments.

^a Reference product is least costly alternative.

The stepped analyses were combined in the CADTH base case. The probabilistic results of the CADTH base case included publicly available prices of the comparator treatments and reflected the Health Canada–indicated population (Table 7). DUP + SOC was \$171,694 more costly and generated 1.26 additional QALYs than SOC. The ICER for DUP + SOC versus SOC was \$136,025 per additional QALY gained. The likelihood that DUP + SOC represented the most cost-effective strategy was 0% if the willingness-to-pay threshold was \$50,000 per QALY (or \$100,000 per QALY).

Notably, 95% of DUP + SOC's total incremental benefit (1.20 of 1.26 QALYS), compared to SOC, was accrued during the extrapolated period (Table 7).

Table 7: Disaggregated Summary of the CADTH Economic Evaluation Results^a

Parameter	DUP + SOC	SOC	Increment	Percentage (%) of total increment ^b
Discounted QALYs				
Total	26.87	25.61	1.26	
By health state				
Decision tree	0.76	0.70	0.06	5.1
Maintenance treatment	5.77	0.00	5.77	457.8
Best supportive care without response	20.28	24.76	-4.48	-355.4
Best supportive care with response	0.06	0.15	-0.09	-7.3
Discounted costs (\$)				
Total	352,98	181,288	171,694	
By cost category				
Active treatment	201,631	0	201,631	117.4
Flare medication	983	1,031	-49	0.0
Other medical	148,835	179,352	-30,517	-17.8
Administration	40	0	40	0.0
Adverse event	1,493	905	588	0.3
ICER	136,025 per QALY gained			

DUP = dupilumab; QALY = quality-adjusted life-year; SOC = standard of care.

Note: The submitted results were based on the publicly available prices of the comparator treatments.

^a The CADTH base case incorporated treatment response outcomes at week 16 from the SOLO trials²³ to estimate DUP + SOC's cost-effectiveness versus SOC in the Health Canada-indicated population.

^b Percentage of total incremental (e.g., the incremental difference within the decision tree is 0.06. When considered in the context of the total incremental difference of 1.26, this equates to 5.1% of the total increment; $0.06/1.26 = 0.051$. The same calculation method was used for the other health states).

Scenario Analysis Results

CADTH undertook price-reduction analyses in the sponsor's base case and in the CADTH base case, assuming proportional price reductions for DUP + SOC (Table 8). To achieve an ICER below \$50,000 per QALY, a price reduction of 54% would be required. However, it should be noted that at this price reduction, there is an 52% likelihood that DUP + SOC is cost-effective.

Table 8: CADTH Price-Reduction Analyses

Price reduction	ICERs for DUP + SOC vs. SOC (\$ per QALY)	
	Sponsor base case	CADTH reanalysis
No price reduction	50,133	136,025
10%	43,094	120,075
20%	36,082	103,768
30%	29,341	88,022
40%	22,090	71,937
50%	15,174	56,107
60%	8,250	40,061

DUP = dupilumab; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years; SOC = standard of care; vs. = versus.

Note: The submitted results were based on the publicly available prices of the comparator treatments.

CADTH performed several analyses on alternate scenarios; including a reassessment of the reimbursement-request population, using EASI-75 as the definition of treatment response, use of the micro-level costing method, and testing alternate estimates of the percentage who sustained treatment response during the extrapolated period (Table 14). CADTH also undertook additional exploratory analyses to present estimates for an alternative outcome (EASI-75) (Table 16). However, the consistency in the results for the moderate and severe populations, despite the differences in treatment response at 16 weeks between the subgroups identified in the trials, suggests that the duration of effect between weeks 16 and 52 has a larger impact on the results.

To estimate DUP + SOC's cost-effectiveness within the scope of the sponsor's reimbursement request, CADTH incorporated AD-1526 data in a scenario analysis (scenario 1; Table 14). DUP + SOC generated additional costs (\$156,469) and QALYs (1.17) compared with SOC. The ICER ratio of DUP + SOC versus SOC was \$133,877 per QALY gained. The same price reduction was required to achieve an ICER below \$50,000 per QALY (Table 15).

CADTH also assessed model features in probabilistic scenario analyses, as reported in Table 14. The ICER decreased by > 10% in the scenarios in which treatment response definition was based on the SOLO trials' pooled EASI-75 outcomes.²³ CADTH incorporated the sponsor's micro-level costing approach, but revised it to have the same frequency of health care visits for all responders; and the percentage who sustained treatment response during the extrapolated period were based on the clinical expert's estimates. The ICER did not change notably in scenarios that explored outcomes in the reimbursement-request population or the impacts of alternative estimates of the percentage who sustained treatment response during the extrapolated period, including the sponsor's submitted values.

Issues for Consideration

- DUP was previously reviewed by CADTH for the treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.²⁴ The CADTH Canadian Drug Expert Committee recommended that DUP not be recommended for use, citing two key reasons. First, no evidence was available that compared DUP with other drugs commonly used in the treatment of AD. Second, there were several notable gaps in the clinical evidence regarding DUP, including data to assess the long-term safety of DUP, concerns with the generalizability of the trial results to patients who would be expected to use DUP in clinical practice, and an absence of efficacy and safety data for the use of DUP in patients for whom topical prescription therapies are not advisable. Furthermore, given differences in the model structure between the original and current submissions, the corresponding results appeared to differ notably for the adult population. However, CADTH noted that the sponsor did not address all of the issues identified as part of the current submission.
- As noted by the clinical expert consulted by this review, there is no clear and objective definition of response. The expert stated that while the EASI score is most likely to be used, several other outcomes (e.g., Investigator's Global Assessment) are used as well.
- Although the Health Canada-approved indication is for DUP to be used as a second-line drug in the treatment of moderate-to-severe AD following inadequate control with topical therapies and as a first-line treatment in patients for whom topical therapies are not advisable, the clinical expert indicated it may in fact be used as a second- or third-line treatment after failing systemic therapy or phototherapy. However, the CADTH clinical review identified limitations with the indirect comparisons that precluded making any

conclusions regarding the comparative clinical effectiveness of DUP + SOC versus these therapies. As the sponsor's model did not allow for this comparison, and clinical review could not reach conclusions on the comparative effectiveness, the potential cost-effectiveness of DUP when compared against these alternative therapies is unknown.

- The sponsor assumed that all patients administered DUP injections independently and were 100% compliant to DUP + SOC treatment. The clinical expert consulted by CADTH suggested that in practice, compliance would be less than 100%, particularly because adolescents would require the assistance of caregivers and are least likely to maintain topical therapy consistently. CADTH was unable to explore the impact of reduced compliance in the model, as this was assumed to affect costs and did not account for the effects on patient outcomes, i.e., treatment-utility or response.

Overall Conclusions

The CADTH appraisal of the sponsor's base case suggests that the reported results were associated with uncertainty for several reasons. The sponsor's estimation of the ICER for DUP + SOC was \$50,133 per QALY gained (2.55 incremental QALYs, \$127,607 incremental costs) compared with SOC. However, this result warranted careful interpretation due to the absence of relevant comparators, the inclusion of data from different trial populations that were then modelled as the same population (which limited the generalizability to the indicated population), the model's inability to facilitate subgroup analysis by disease severity, the use of uncertain measures to approximate the durability of treatment response, the use of utility estimates that lacked face validity and included caregiver-related disutilities, and the use of frequencies of health resource use that were not reflective of Canadian practice.

After addressing these issues in the CADTH reanalysis as comprehensively as possible, the decision uncertainty surrounding DUP + SOC's relative value over SOC was substantial across the Health Canada–indicated and reimbursement-request populations. In the CADTH base case, which reflected the indicated population, the ICER for DUP + SOC versus SOC was \$136,025 per QALY gained. The corresponding ICER in the scenario analysis that addressed the reimbursement-request population was similar, at \$133,877 per QALY gained. The probability that DUP + SOC represented the optimal strategy was 0% at willingness-to-pay thresholds of \$50,000 and \$100,000 per QALY in both analyses. A reduction of 54% in DUP's price was required to improve its cost-effectiveness, relative to SOC, in both populations and generate an ICER of less than \$50,000 per QALY (indicated: \$49,648 per QALY gained; reimbursement request: \$48,681 per QALY gained).

Nonetheless, the results of the reanalysis, which were based on publicly available prices, remain uncertain as multiple limitations could not be addressed. CADTH was unable to assess the cost-effectiveness of DUP + SOC compared to alternative comparators that are presently used by patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies; nor was it possible to determine how DUP's cost-effectiveness differed in patients with moderate AD versus those with severe AD. Results of additional scenario and exploratory analyses highlighted that the durability of effect between weeks 16 and 52 is a key driver of the model and has a greater impact than that of initial treatment response.

Appendix 1: Cost Comparison Table

The comparators presented in Table 9 have been deemed to be appropriate based on feedback from clinical experts. Comparators may be recommended (appropriate) practice or actual practice. Existing product listing agreements are not reflected in the table and as such, may not represent the actual costs to public drug plans.

Table 9: CADTH Cost Comparison Table for Systemic Treatments for Atopic Dermatitis

Drug/comparator	Strength	Dosage form	Price (\$)	Recommended dosage	Cost per day (\$)	Cost per course (\$)
Dupilumab (Dupixent)	200 mg/1.14 mL 300 mg/2 mL	Pre-filled syringe	\$959.9350 ^a	Adults: 600 mg as an initial dose, followed by 300 mg every two weeks Adolescents < 60 kg: 400 mg as an initial dose, followed by 200 mg every two weeks Adolescents ≥ 60 kg: 600 mg as an initial dose, followed by 300 mg every two weeks	First year: 68 Each subsequent year: 71	First year: 25,918 Each subsequent year: 24,958
Immunosuppressants						
Azathioprine (generic)	50 mg	Tablet	0.2405	<i>Pediatric:</i> 1.0 to 4.0 mg/kg per day for 24 weeks <i>Adult:</i> 1.0 to 3.0 mg/kg per day for 24 weeks	<i>Pediatric:</i> 0.24 to 0.96 ^c <i>Adult:</i> 0.24 to 0.96 ^d	<i>Pediatric:</i> 40 to 162 <i>Adult:</i> 40 to 162
Cyclosporine (generic)	10 mg 25 mg 50 mg 100 mg	Caplet	0.6520 0.9952 1.9400 3.8815	<i>Pediatric:</i> 3.0 to 6.0 mg/kg per day for 24 weeks <i>Adult:</i> 150 to 300 mg per day for 24 weeks	<i>Pediatric:</i> 3.88 to 11.64 ^c <i>Adult:</i> 7.76 to 19.56 ^d	<i>Pediatric:</i> 652 to 2,957 <i>Adult:</i> 1,304 to 3,286
Methotrexate (generic)	2.5 mg	Tablet	0.6325	<i>Pediatric:</i> 0.2 to 0.7 mg/kg per week for 24 weeks <i>Adult:</i> 7.5 to 25 mg per week for 24 weeks	<i>Pediatric:</i> 2.28 to 7.97 ^c per week <i>Adult:</i> 1.90 to 6.33 per week	<i>Pediatric:</i> 55 to 191 <i>Adult:</i> 46 to 152
Mycophenolate mofetil	250 mg 500 mg	Caplet	0.3712 0.7423	<i>Pediatric:</i> 30.0 to 50.0 mg/kg per day for 24 weeks <i>Adult:</i> 1.0 to 1.5 g twice daily for 24 weeks	<i>Pediatric:</i> 0.50 to 3.34 ^c <i>Adult:</i> 2.23 to 2.97	<i>Pediatric:</i> 84 to 561 <i>Adult:</i> 374 to 499

Drug/comparator	Strength	Dosage form	Price (\$)	Recommended dosage	Cost per day (\$)	Cost per course (\$)
Other treatments for adults not specifically indicated for the treatment of atopic dermatitis						
Acitretin (Soriatane)	10 mg 25 mg	Caplet	1.2965 2.2770	10 to 50 mg once daily, maximum of 75 mg once daily for 24 weeks	1.30 to 6.83	218 to 1,148
Alitretinoin (Toctino)	10 mg 30 mg	Caplet	21.9900	30 mg once daily, dose may be reduced to 10 mg if unacceptable side effects for 24 weeks	21.99	3,694
Apremilast (Otezla)	10 mg/20 mg 30 mg	Tablet	19.5715 ^b	30 mg twice daily, starting with titration pack (27 tablet kit titrating from 10 mg once daily to 30 mg twice daily)	19.57 to 39.14	First year: 14,268 Each subsequent year: 14,287
Ustekinumab (Stelara)	45 mg/0.5 mL 90 mg/1 mL	Pre-filled syringe	4593.1400	45 mg at weeks 0 and 4 and then every 12 weeks thereafter, 90 mg may be used for patients > 100 kg in weight	54.53	First year: 27,559 Each subsequent year: 19,904 to 39,807

Note: Unit prices of medications are taken from the Ontario Drug Benefit Formulary¹² (accessed October 2019), unless otherwise indicated. Recommended doses from respective product monographs, unless otherwise indicated. Annual period assumes 52 weeks, or 13 x 4 weeks per year (365 days for all comparators).

Note: According to the CADTH clinical expert consulted for this review, retinoids are primarily used to treat hand dermatitis in adults, not in adolescents.

^a Sponsor's submitted price for each dosage.

^b IQVIA Delta PA¹³ wholesale price (retrieved January 2019).

^c Assumes child weight of 45 kg.

^d Assumes adult weight of 70 kg.

In addition, according to the clinical expert consulted as part of this review, the following topical treatments and phototherapy from the 2014 American Academy of Dermatology's Guidelines of Care for the Management of Atopic Dermatitis^{25,26} may be used to treat moderate-to-severe AD in adolescents and adults despite not being indicated (Table 10).

Table 10: CADTH Cost Comparison Table for Topical Treatments for Atopic Dermatitis

Drug/comparator	Strength	Package size	Dosage form	Price per gram (\$)	Recommended dosage
Topical corticosteroids					
Amcinonide (generics)	0.1%	60 g tube 60 mL bottle 60 g tube	Cream Lotion Ointment	0.1955 0.2997 ^a 0.3069 ^a	Thin amount to affected area twice daily, max 5 days on face, axillae, scrotum or scalp, two to three weeks elsewhere
Betamethasone dipropionate (generic)	0.05%	50 g tube 60 g bottle 75 mL bottle 50 g tube	Cream Foam Lotion Ointment	0.2048 1.5746 ^b 0.1980 0.5186	Thin film to affected area twice daily, duration of therapy varies; need should be reassessed at least every 4 weeks
Betamethasone valerate (generic)	0.1%	450 g jar 30 mL, 60 mL bottles 450 g jar	Cream Lotion Ointment	0.0889 0.3125 0.0889	No recommended daily dose; use as directed by clinicians

Drug/comparator	Strength	Package size	Dosage form	Price per gram (\$)	Recommended dosage
Clobetasol propionate (generic)	0.05%	15 g, 50 g tubes, 450 g jar 15 g, 50 g tubes	Cream Ointment	0.2279 0.2279	Thin amount to affected area twice daily; weekly application should not exceed 50 g, and limited to two consecutive weeks
Desonide (generic)	0.05%	15 g, 60 g tubes, 454 g jar 60 g tube	Cream Ointment	0.2650 0.2647	Thin amount to affected area twice daily; may be increased in refractory cases
Desoximetasone (Topicort)	0.25% 0.25% 0.5%	20 g, 60 g tubes 60 g tube 15 g, 60 g tubes	Cream Ointment Gel	0.7340 ^a 0.7142 ^a 0.5540 ^a	Thin amount to affected area twice daily
Fluocinonide (Lyderm, Lidex)	0.05%	15 g, 60 g tubes, 400 g jar 15 g, 60 g tubes 15 g, 60 g tubes	Cream Gel Ointment	0.2378 0.3076 0.3035	Thin amount to affected area twice daily; weekly application should not exceed 45 g and limited to two weeks
Fluocinonide (Tiamol)	0.05%	25 g tube 100 g jar	Emol Cream	0.1980	Thin amount two to four times daily
Halobetasol propionate (Ultravate)	0.05%	15 g, 50 g tubes 50 g tube	Cream Ointment	1.1130 ^c 0.0811 ^c	Thin amount to affected area twice daily; limited to 50 g weekly and two weeks without re-evaluation
Hydrocortisone (various)	1.0%	45 g tube	Cream	0.1718	No recommended daily dose; use as directed by clinicians
	1.0% 2.5%	60 mL bottle	Lotion	0.1587 0.2100	
	0.5% 1.0%	15 g tube 454 g jar	Ointment	0.1400 0.0390	
Hydrocortisone acetate	0.5% 1.0%	15 g, 30 g tubes 28.4 g tube	Cream Ointment	0.2056 0.4158 ^c	Twice-daily application is generally recommended initially; intermittent use 1 to 2 times per week on areas that commonly flare for maintenance therapy
Hydrocortisone valerate (Hydroval)	0.2%	15 g, 45 g, 60 g tubes 15 g, 60 g tubes	Cream Ointment	0.1313	Small amount to affected area twice daily; discontinue as soon as lesions heal or if no response
Mometasone furoate (generic)	0.1%	15 g, 50 g tubes 15 g, 50 g tubes	Cream Ointment	0.5542 0.2252	Thin film to affected areas twice daily
Triamcinolone acetonide (various)	0.1%	30 g tube 15 g tube	Cream Ointment	0.0533	No recommended daily dose; use as directed by clinicians

Drug/comparator	Strength	Package size	Dosage form	Price per gram (\$)	Recommended dosage
Topical calcineurin inhibitors					
Pimecrolimus (Elidel)	1%	10 g, 30 g tubes	Cream	2.4157	Thin layer to affected area twice daily; discontinue when resolved or after three weeks if no improvement or exacerbation
Tacrolimus	0.03% 0.10%	30 g tube	Cream	2.3740 2.5397	Thin layer to affected area twice daily; discontinue after six weeks if no improvement or exacerbation
Phosphodiesterase type-4 inhibitor					
Crisaborole (Eucrisa)	2%	60 g tube	Ointment	2.3000 ^d	Thin layer to affected area twice daily
Phototherapy					
Ultraviolet light therapy	NA	NA	NA	7.85 per treatment ^e	3 to 5 treatments per week ^f

emol = emollient; NA = not available.

^a Saskatchewan Formulary list price²⁷ (December 2019).

^b Alberta Formulary list price²⁸ (December 2019).

^c British Columbia Formulary list price²⁹ as reported by IQVIA Delta PA (January 2019).

^d Crisaborole received a recommendation of do not reimburse from the CADTH Canadian Drug Expert Committee in March 2019 for treatment of mild-to-moderate AD in patients two years of age and older who have failed or are intolerant to a topical corticosteroid treatment.^{30,31}

^e Ontario Schedule of Benefits for Physician Services, code G470 "Ultraviolet Light Therapy," accessed December 2019.¹³

^f Minimum frequency of phototherapy sessions required per week for successful maintenance as well as length of maintenance period varies tremendously between individuals.^{25,26}

Source: Ontario Drug Benefit Formulary list prices¹⁴ unless otherwise indicated, recommended doses from respective product monographs unless otherwise indicated.

Appendix 2: Submission Quality

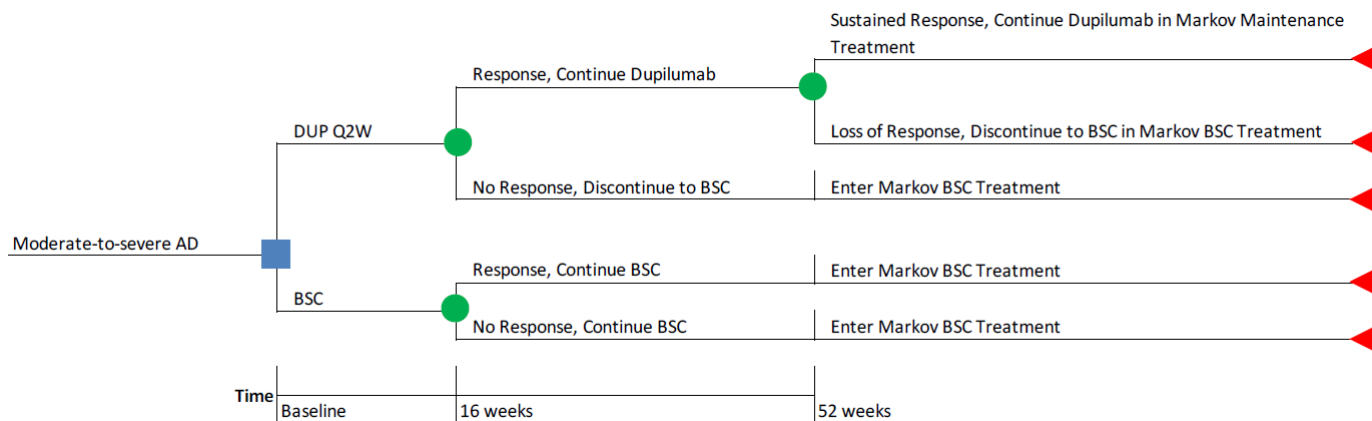
Table 11: Submission Quality

	Yes	No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The sponsor included one relevant comparator, i.e., standard of care, but was missing several others. The population had limited generalizability to the indicated population. See “CADTH Appraisal of the Sponsor’s Economic Evaluation” for details.
Model has been adequately programmed and has sufficient face validity.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	The model was generally adequately programmed.
Model structure is adequate for the decision problem.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	While the model structure was adequate for the decision problem, the chosen structure lacked the flexibility to capture the waxing and waning nature of atopic dermatitis. The model assumed that patients remaining on DUP + SOC treatment were constantly responding, and that treatment stopped immediately from the point in time that response was lost. A model that considered severity should have been presented. See “CADTH Appraisal of the Sponsor’s Economic Evaluation” for details.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	The model varied most parameters relevant to the decision problem in a probabilistic analysis. For example, parameter distributions were not assigned to the resource-use event rates and incidence of adverse events, which were modelled as point estimates. Also, the model did not account for health care costs incurred by patients who develop a marginal treatment response.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	The model sufficiently captured parameter and structural uncertainty, with some exceptions. Measures of relative risk and corresponding standard errors were calculated incorrectly. Also, the model also did not capture the effects of treatment compliance adequately (see “CADTH Appraisal of the Sponsor’s Economic Evaluation”).
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	The report was generally coherent, but had notable gaps in the information it presented about the model. For instance, the report did not define topical therapies in standard of care and lacked adequate detail on the source of select model inputs (e.g., estimates used to derive the “relative risk” of sustained treatment response until week 52). Furthermore, the report did not provide justification for the use of certain formulas for the DUP + SOC comparator and others for the SOC comparator (e.g., approach for modelling the percentage who sustained a 52-week response).

DUP = dupilumab; SOC = standard of care.

Appendix 3: Additional Information on the Submitted Economic Evaluation

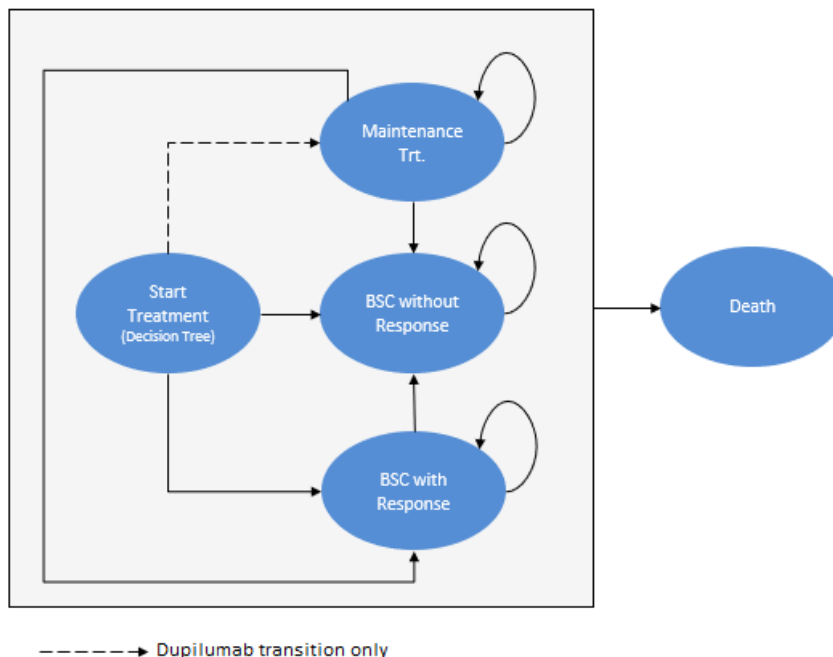
Figure 1: Decision Tree



AD = atopic dermatitis; BSC = best supportive care; DUP Q2W = dupilumab every 2 weeks.

Source: Sponsor's pharmacoeconomic submission.¹

Figure 2: Markov Structure



Trt. = treatment; BSC = best supportive care.

Source: Sponsor's pharmacoeconomic submission.¹

Detailed Results of the Sponsor’s Submission

Table 12: Probabilistic Results of Sponsor’s Base-Case Analysis

Parameter	DUP + SOC	SOC	Increment	Percentage (% of total increment)
Discounted QALYs				
Total	26.22	23.67	2.55	
By health state				
Decision tree	0.83	0.72	0.11	4.3
Maintenance treatment	6.11	0.00	6.11	239.6
Best supportive care without response	19.26	22.89	-3.63	-142.4
Best supportive care with response	0.03	0.06	-0.03	-1.2
Discounted costs (\$)				
Total	486,163	358,555	127,607	
By cost category				
Active treatment	177,333	0	177,333	139.0
Flare medication	985	1,027	-42	0.0
Other medical	306,375	356,622	-50,247	39.4
Administration	40	0	40	0.0
Adverse event	1,430	906	524	0.4
Incremental cost-effectiveness ratio	\$50,133 per QALY gained			

DUP = dupilumab; QALY = quality-adjusted life-year; SOC = standard of care.

Note: Total expected life-years (43.04 years) were derived from the deterministic analysis, but likely do not differ between comparators given that the total expected QALYs that were estimated in the probabilistic analysis were similar (DUP + SOC = 26.22; SOC = 23.67).

Source: Sponsor’s pharmacoeconomic submission.

Table 13: Probabilistic Results of Sponsor’s Scenario Analyses

Scenario	ICER (\$ per QALY)
1 Baseline utility values based on sponsor’s unpublished study of EQ-5D data among children with AD	60,893
2 Discount rate of 0%	49,191
3 Discount rate of 3%	50,400
4 Included cost for self-injection training with a nurse for one hour	49,902
5 Patients who could no longer use systemic immunosuppressant therapies	52,168
6 Rate of discontinuing dupilumab use was 0%	50,065
7 Rate of discontinuing dupilumab use was 12.3%	49,922
8 Response definition was based on EASI-50 and DLQI ≥ 4	51,341
9 Response definitions was based on EASI-75	50,876
10 Societal perspective	35,778
11 SOLO trial’s subgroup of adults whose mean age was 34 years	57,419
12 SOLO trial’s subgroup of adults whose mean age was 34 years and all patients who could no longer use systemic immunosuppressant therapies	57,991
13 Sustained response only among patients taking dupilumab plus standard of care	49,178
14 Time horizon was 10 years	50,479
15 Time horizon was 5 years	51,918

AD = atopic dermatitis; DLQI = Dermatology Life Quality Index; EASI-50 = Eczema Area and Severity Index score improvement from baseline ≥ 50%; EASI-75 = Eczema Area and Severity Index score improvement from baseline ≥ 75%; EQ-5D = EuroQol 5-Dimensions; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Source: Sponsor’s pharmacoeconomic submission.¹

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Scenario Analyses

Table 14: Probabilistic Results of the CADTH Scenario Analyses

	Scenario	ICER (\$/QALY)
1	Treatment response outcomes at week 16 sourced from AD-1526 to capture the reimbursement-request population	133,877
2	Treatment response definition based on the SOLO trials' pooled EASI-75 outcomes ²³	120,738
3	Incorporated micro-costing approach based on same number of dermatology visits for all responders	115,148
4	Sponsor's submitted estimates of the percentage who sustained treatment response during extrapolated period in DUP + SOC and SOC	135,434
5	Percentage who sustained treatment response during the extrapolated period among patients on DUP + SOC (year 2: 90%; year 3: 80%; year 4: 70%; year 5+: 60%)	146,608
6	Clinical expert's estimates of the percentage who sustained treatment response during extrapolated period in DUP + SOC (year 2: 90%; year 3: 80%; year 4: 70%; year 5+: 60%) and SOC (year 2: 80%; year 3: 60%; year 4: 40%; year 5+: 20%)	150,854

DUP = dupilumab; EASI-75 = Eczema Area and Severity Index score improvement from baseline \geq 75%; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care.

Table 15: Additional CADTH Price-Reduction Analyses – Reimbursement-Request Population

ICERs for DUP + SOC vs. SOC (\$ per QALY)			
Price reduction	Sponsor base case	Sponsor scenario for reimbursement-request population	CADTH scenario for reimbursement-request population ^a
No price reduction	50,133	52,168	133,877
10%	43,094	43,562	117,985
20%	36,082	36,315	102,320
30%	29,341	29,761	86,661
40%	22,090	22,906	70,911
50%	15,174	15,158	55,083
60%	8,250	8,375	39,350

DUP = dupilumab; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years; SOC = standard of care; vs. = versus.

Note: The submitted results were based on the publicly available prices of the comparator treatments.

^aCADTH scenario 1 incorporated treatment response outcomes at week 16 from the AD-1526 trial⁹ to estimate DUP + SOC's cost-effectiveness vs. SOC in the reimbursement-request population.

Table 16: Probabilistic results of the CADTH Exploratory Analyses by Disease Severity

	Scenario	ICER (\$ per QALY)
1	Treatment response definition based on the SOLO 1 trial's EASI-75 outcomes at week 16 and the CHRONOS trial's EASI-75 outcomes at week 52; restricted to patients with <u>moderate AD</u>	121,639
2	Treatment response definition based on the SOLO 1 trial's EASI-75 outcomes at week 16 and the CHRONOS trial's EASI-75 outcomes at week 52; restricted to patients with <u>severe AD</u>	121,306
3	Treatment response definition based on the CHRONOS trial's EASI-75 outcomes at week 16 and 52; restricted to patients with <u>moderate AD</u>	123,220
4	Treatment response definition based on the CHRONOS trial's EASI-75 outcomes at week 16 and 52; restricted to patients with <u>severe AD</u>	118,723

AD = atopic dermatitis; EASI-75 = Eczema Area and Severity Index score improvement from baseline $\geq 75\%$; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: Treatment effects derived from Appendix 3 in the CADTH Clinical Report.

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