CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Dupilumab (DUPIXENT)

(Sanofi-Aventis Canada Inc.)

Indication: Moderate-to-severe atopic dermatitis (AD)

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

CDR	CADTH Common Drug Review
CUA	cost-utility analysis
EASI	Eczema Area and Severity Index
HRQoL	health-related quality of life
ICUR	incremental cost-utility ratio
IGA	Investigator's Global Assessment
LOCF	last observation carried forward
QALY	quality-adjusted life-year
RCT	randomized controlled trial
SOC	standard of care
TCI	topical calcineurin inhibitor
TCS	topical corticosteroids

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Dupilumab (Dupixent)
Study Question	From the perspective of the publicly funded health care payer, what is the incremental cost-effectiveness of dupilumab compared with available treatments in adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies
Treatment	Dupilumab 600 mg subcutaneous loading dose and then every two weeks plus SOC, defined as mid-potency topical corticosteroids or topical calcineurin inhibitors
Outcome(s)	QALYs
Comparator(s)	SOC: mid-potency topical corticosteroids or topical calcineurin inhibitors
Perspective	Canadian publicly funded health care payer
Time Horizon	Lifetime (63 years in the base case)
Results for Base Case	ICUR = $89,723[a]
Key Limitations	CDR identified several key limitations with the submitted analysis: • The manufacturer's analysis excluded relevant comparators. Patients who are unresponsive to topical pharmacotherapies are most likely to be prescribed an immunosuppressant off-label, such as methotrexate and cyclosporine, used intermittently due to their potential toxicities. In addition, alitretinoin is indicated for hand dermatitis and may be used for dermatitis involving other sites. CDR could not test this limitation because of limited data on the comparative effectiveness between therapies. • The manufacturer assumed that 81.7% of patients are compliant with dupilumab, which reduces drug-treatment costs, but had no effect on quality of life or treatment response. The effects of compliance were not fully incorporated within the model. Given the limited data on the impact of compliance on treatment effectiveness, CDR conducted a reanalysis, setting compliance to 96.89%. • Treatment-specific utility values were applied with insufficient description of the methods behind the regression analysis to derive utility weights. This deviates from best practice guidelines that recommend utility weights based on health states. It is not clear why this approach was taken, and the use of regression analysis to determine treatment-specific utility weights may have introduced bias in favour of dupilumab plus SOC. Furthermore, patients on dupilumab plus SOC were assumed to maintain their quality of life throughout the duration of treatment without adequate justification. CDR conducted a reanalysis using the change in HRQoL that was reported in the trial and assuming identical rates of treatment waning for both treatment arms. • The discontinuation rate used for dupilumab was lower than reported for other biologics and in the SOLO trial, favouring dupilumab. CDR conducted a reanalysis assuming the discontinuation rate for dupilumab as reported in the SOLO trial in order to better align with the reported discontinuation rates observed with other biologic treatments for chronic inflammatory skin disease. • It was not possible to assess the cost-effectiveness of dupilumab plus SOC in patients where topical prescription therapies are not advisable.

CDR Estimate(s)	In revising the discontinuation rate, compliance rate, and health-state utility values: • The CDR base case for dupilumab plus SOC, when compared with SOC alone in patients whose disease is not adequately controlled by topical prescription therapies, resulted in an ICUR of $579,672 per QALY gained. • A price reduction of 84% is required for dupilumab plus SOC to be cost-effective at a willingness-to-pay threshold of $50,000 per QALY in patients whose disease is not adequately controlled with topical prescription therapies.

CDR = CADTH Common Drug Review; HRQoL = health-related quality of life; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SOC = standard of care.

[a] Not reported but calculated from manufacturer model.

Drug	Dupilumab (Dupixent)
Indication	For the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab can be used with or without topical corticosteroids.
Reimbursement Request	As per indication
Dosage Form(s)	Solution for subcutaneous injection
NOC Date	30-11-17
Manufacturer	Sanofi-Aventis Canada Inc.

Executive Summary

Background

Dupilumab (Dupixent) is indicated for use in adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.[1] Dupilumab can be used with or without topical corticosteroids (TCS). The dosage form is 150 mg/mL solution in a pre-filled syringe, intended for patients to self-administer subcutaneously.[1] The recommended dosage for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg injected every other week.[1] At the submitted price of $1,153.85 per 300 mg dose,[2] the first-year cost of dupilumab is $31,154, and $30,000 annually thereafter.

The manufacturer submitted a cost-utility analysis (CUA) of dupilumab as an add-on to current standard of care (SOC) in patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies. SOC was defined as mid-potency TCS or topical calcineurin inhibitors (TCIs). The base-case analysis was conducted from the perspective of the Canadian publicly funded health care payer over a lifetime time horizon (63 years), with future costs and benefits discounted at 1.5 % per annum.[2] The model structure included a short-term (one-year) phase in which efficacy was modelled in terms of responder status based on the results of the LIBERTY AD CHRONOS trial,[3] and a long-term maintenance phase consisting of three health states: on maintenance treatment with dupilumab and SOC; on treatment with SOC alone; and death.[2] In the maintenance phase, patients on dupilumab plus SOC may remain on treatment, discontinue dupilumab and transition to SOC, or die, whereas patients on SOC alone were modelled as remaining on SOC until death.[2] Treatment-specific utilities were obtained through a mixed-model regression based on the LIBERTY AD CHRONOS trial. Resource use and costs were collected from both published literature and an unpublished study undertaken by the manufacturer.[4,5]

In their probabilistic base case, the manufacturer estimated that the addition of dupilumab to SOC versus SOC alone would produce an additional 1.25 quality-adjusted life-years (QALYs) for an additional $112,362 per person treated, resulting in an incremental cost per QALY of $89,723.[2] In this analysis, dupilumab plus SOC had a 0.1% probability of being cost-effective at a $50,000 per QALY threshold.[2]

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several key limitations with the model submitted by the manufacturer.

Based on feedback from the clinical expert consulted for this review, patients who are unresponsive to topical pharmacotherapies are most likely to be prescribed an immunosuppressant (off-label treatment) such as methotrexate and cyclosporine. These off-label treatments are generally used only intermittently due to the possible toxicities. In addition, alitretinoin is indicated for hand dermatitis and may be used for dermatitis involving other sites. CDR could not assess the comparative cost-effectiveness of dupilumab plus SOC compared with these alternative therapies because of a lack of data on the comparative clinical effectiveness between these therapies.

Furthermore, there were a number of assumptions regarding the utility values that directly impact the cost-effectiveness of dupilumab. The manufacturer considered utility weights based on treatment rather than by model health states. This is not considered best practice in modelling.[6] In addition, treatment-specific utility values were estimated by regression analysis and the methods were poorly described. It is difficult to assess the appropriateness of this approach and it may have overestimated the utility gain for those on dupilumab. Given the relatively short duration of the available clinical trials, the durability of the treatment effect with respect to patients' utility on dupilumab has not been well established (i.e., no information to suggest that the clinical effects will persist over a patient's lifetime). In the model, responders to dupilumab plus SOC were assumed to maintain their treatment effects over their lifetime, whereas the treatment effects on SOC alone were assumed to wane after the first year. Long-term data to support these assumptions are lacking. According to the clinical expert consulted as part of this CDR review, disease severity is expected to wax and wane over time, independent of treatment, and patients may be more motivated to adhere to treatment during periods of flares.[7]

Other limitations identified by CDR for this submission included assumptions regarding compliance with dupilumab. The manufacturer assumed compliance on dupilumab would decrease to 81.7% after the first 16 weeks of treatment, resulting in lowered drug costs associated with dupilumab without impacting treatment efficacy or quality of life.[2] Finally, modelling treatment discontinuation based on the LIBERTY AD CHRONOS trial[3] may have overestimated the number of patients remaining and responding to dupilumab treatment over the long term.

Lastly, the economic analysis was unable to assess the cost-effectiveness of dupilumab in patients where topical prescription therapies would not be advisable, as there was limited clinical data on this patient population. The clinical expert consulted for the CDR review noted that this is expected to represent a small portion of patients who would be receiving dupilumab.

CDR attempted to address many of the above limitations by: conducting a reanalysis that used a different approach to determine utility values (based on the utility change observed in the LIBERTY AD CHRONOS trial,[3] and assuming less optimistic treatment waning); limiting the effects of compliance (by using the trial reported compliance of 96.89%); and revising rates of discontinuation for dupilumab (to reflect the rates reported in the SOLO trials[8,9]). This resulted in an incremental cost-utility ratio (ICUR) for dupilumab plus SOC of $579,672 per QALY when compared with SOC alone in patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies.

Conclusions

In patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies, CDR estimates an ICUR of $579,672 per QALY for dupilumab plus SOC compared with SOC alone. The difference in incremental utilities was largely driven by the approach taken to model utilities and the assumptions around the waning of the treatment effect for both treatment arms in the model. The model was sensitive to both sets of assumptions.

A price reduction of 84% would be required for the ICUR of dupilumab plus SOC to fall below the $50,000 per QALY when compared with SOC alone. CADTH was unable to assess the cost-effectiveness of dupilumab plus SOC compared with alternative comparators that are presently used by patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies. The magnitude of clinical benefit dupilumab may offer compared with these alternative treatments remains uncertain, given the lack of comparative effectiveness evidence.

CADTH notes that this model does not explicitly address the population of patients for whom topical therapies are not advisable, and the ICUR is presently unknown in this patient population.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis (CUA) comparing dupilumab plus standard of care (SOC) compared with SOC alone in adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies.[2] Standard of care was defined as mid-potency topical corticosteroids (TCS) or topical calcineurin inhibitors (TCIs). The model used a lifetime horizon (63 years) from the perspective of the publicly funded health care payer, with costs and clinical outcomes (QALYs) discounted at 1.5% per annum.[2] The model reflected a population that had baseline characteristics similar to the LIBERTY AD CHRONOS trial (58.7% males; average age: 37.6).[3] The model structure included a short-term (one-year) phase for the 16- and 52-week assessment in the LIBERTY AD CHRONOS trial, and a lifetime model for the maintenance phase. The short-term phase was based on a decision tree that modelled treatment response at 16 weeks and 52 weeks. The maintenance phase was based on a Markov state–transition model with annual cycles and consisted of three health states: on maintenance treatment with dupilumab plus SOC, on SOC, and death.[2]

All patients started in the trial phase as a nonresponder and, at 16 weeks, patients were evaluated for treatment response. In the manufacturer's base-case analysis, responders were defined as those who do not use a systemic immunosuppressant (such as methotrexate) and achieve an Investigator's Global Assessment (IGA) end point of 0 or 1, with a reduction from baseline of two or more points. In the dupilumab arm, those who responded to treatment stayed on dupilumab until 52 weeks, at which point nonresponders discontinued dupilumab, as reported in the LIBERTY AD CHRONOS trial[3] All nonresponders were treated with SOC alone. The proportion of patients entering each health state in the Markov model was therefore based on the patients' treatment response at 16 weeks and 52 weeks. In the maintenance phase, patients may discontinue dupilumab and transition to SOC. In the SOC-alone arm, it was assumed that all patients remained on SOC during the maintenance phase.[2]

The manufacturer assumed no mortality effect from treatment; all treatment benefits were captured by an improvement in health-related quality of life (HRQoL).[2] Treatment-specific utilities were estimated for dupilumab plus SOC and SOC alone, rather than employing state-specific utilities. The regression was based on data from the LIBERTY AD CHRONOS trial using a mixed-model regression analysis. A forward-selection process was used to determine best fit and resulted in the following regression covariates: age, male, baseline EuroQol 5-Dimensions questionnaire (EQ-5D), total Eczema Area Severity Index (EASI) score, the weekly average of peak daily pruritus, EASI–pruritus interaction, and a treatment dummy.[2] The model assumed no decrement in utility due to adverse events.[2]

The model included acquisition costs of dupilumab, medical costs relating to responder status, and the costs of treating adverse events.[2] Drug costs were obtained from the manufacturer based on a 600 mg loading dose and a 300 mg dose every two weeks thereafter. It was assumed that patients would not be fully compliant to dupilumab from 16 weeks onward, resulting in lower drug-treatment costs.[2] SOC was not costed to avoid issues of double counting, given that health state–specific costs were present in the model based

on responder status.[2] The manufacturer assumed that the administration cost, specifically, the cost of training patients to administer subcutaneous injections, would be covered by the manufacturer through a patient support program.[2] Other medical costs were attributed to responders and nonresponders based on unpublished studies undertaken by the manufacturer.[4,5] The costs of treatment-specific adverse events included a one-time injection-site reaction and other adverse events (e.g., rates of allergic conjunctivitis, infectious conjunctivitis, and oral herpes) were modelled by per-cycle incidence rates.[2]

Manufacturer's Base Case

Dupilumab plus SOC was found by the manufacturer to be $112,362 more expensive than SOC alone. The estimated benefit of dupilumab plus SOC was an additional 1.25 QALYs over 64 years.[2] Table 2 shows the contribution of the different sources of cost to the overall total costs (the results are deterministic, as they were not reported for the probabilistic analysis). In the probabilistic base case, the incremental cost-effectiveness of using dupilumab plus SOC compared with SOC alone is $89,723 per additional QALY gained. Based on the manufacturer's probabilistic sensitivity analysis, SOC had 99.9% probability of being the most likely cost-effective option at a cost-effectiveness threshold of $50,000 per QALY.[2]

Table 2: Summary of Results of the Manufacturer's Base Case

	Deterministic Results			Probabilistic Results		
	Dupilumab + SOC (a)	SOC (b)	Difference ($a-b$)	Dupilumab + SOC (d)	SOC (e)	Difference ($d-e$)
QALYs	22.20	21.06	1.14	22.31	21.06	1.25
Cost ($)						
Drug acquisition costs	120,326	0	120,326	NR	NR	
Other medical costs	112,279	129,133	−16,855	NR	NR	
Adverse event costs	115	92	23	NR	NR	
Administration costs	0	0	0	NR	NR	
Total costs	232,720	129,225	103,495	241,528	129,166	112,362
ICUR ($/QALY)			90,785 [a]			89,723[a]

ICUR = incremental cost-utility ratio; NR = not reported; QALY = quality-adjusted life year; SOC = standard of care.
[a] Not reported but calculated from manufacturer model.
Source: Manufacturer pharmacoeconomic submission.[2]

Summary of Manufacturer's Sensitivity Analyses

Uncertainty was addressed using a Monte Carlo simulation, one-way deterministic sensitivity analyses, and scenario analyses. Based on the manufacturer's one-way deterministic sensitivity analyses, the results were most sensitive to compliance to dupilumab during the maintenance phase, baseline utility weight, and dupilumab drug costs.[2]

Scenario analyses were used to consider a broader societal perspective, the effect of different measurements to define treatment response, different approaches to calculate treatment-specific utility values, shorter time horizons, and using the SOLO trial as an alternative data source.[2] The model results were most sensitive to the time horizon used, with shorter time horizons resulting in a larger ICUR. Reduction of the time horizon to 16 weeks resulted in an ICUR of $923,203 per QALY and, with a one-year time horizon to reflect the LIBERTY AD CHRONOS trial period, the ICUR was $467,208 per QALY. Use of

different approaches to define treatment-specific utility weights resulted in a range of ICURs, with the approach taken in the manufacturer's base case (regression, last observation carried forward [LOCF]) presenting the lowest ICUR ($89,723), increasing to $143,890 per QALY when utility weights were based on the observed change in baseline from the LIBERTY AD CHRONOS trial without using LOCF. An analysis that included productivity losses and out-of-pocket expenses reduced the ICUR to $62,279 per QALY. [redacted] compared with the CHRONOS trial population, which only recruited patients who were inadequately controlled with topical therapies. However, the SOLO trial restricted treatment to dupilumab monotherapy, as patients were not permitted to use supportive therapies. Results from the SOLO trial resulted in an ICUR of $95,639 per QALY.[2]

The results of these analyses suggest that parameters pertaining to time (i.e., horizon and long-term extrapolation of clinical benefits) and utility weights had the largest impact on the ICUR.

Limitations of Manufacturer's Submission

1) **Missing all clinically relevant comparators:** Current SOC in Canada includes the use of systemic immunosuppressants such as methotrexate and cyclosporine. The benefits and costs of using these treatments have not been included in the model, although the LIBERTY AD CHRONOS trial did allow the use of these treatments in both treatment arms. The inclusion of systemic immunosuppressants in the model would likely increase the ICUR for dupilumab plus SOC, i.e., making dupilumab plus SOC less cost-effective. These treatments are much less expensive than dupilumab and are used widely to improve the health of patients with atopic dermatitis and other dermatological conditions. The CADTH Common Drug Review (CDR) was unable to conduct a reanalysis to assess the comparative cost-effectiveness of dupilumab plus SOC compared with these comparators, given the lack of comparative clinical effectiveness data. Annual or treatment-cycle costs of relevant therapies for atopic dermatitis are presented in Appendix 1.

2) **Modelling the impact of compliance with dupilumab:** The manufacturer inconsistently applied the impact of compliance into the model. In the manufacturer's submitted model, it was assumed that 81.7% of responders would remain compliant to dupilumab treatment from week 16 onwards.[2] This was implemented in the model by decreasing the costs of dupilumab with no effects on patient outcomes, i.e., treatment utility or response.[2] The approach taken by the manufacturer is optimistic as, although it may provide a more realistic cost estimate, it likely overestimates the absolute benefit of dupilumab. To match the effect of decreased compliance on costs and treatment effect, CDR used the reported compliance of 96.89% from the LIBERTY AD CHRONOS trial

3) **Estimates of treatment-specific utility values:** As per current guidelines for the conduct of economic evaluations,[6] utilities should reflect the health states within the model and not be specific to treatment. No justification was provided in support of the use of treatment-specific utilities.

   Treatment-specific utility values were derived from a mixed-model regression analysis.[2] It was not clear why some variables were excluded from the forward-

selection process, in particular, why the Dermatology Life Quality Index (DLQI) was not tested in the model, and how the utility weights were estimated (i.e., which values for the Pruritus Numerical Rating Scale and EASI were multiplied by the model coefficients to estimate the utility for each treatment). A request was made to the manufacturer for further information on how the regression model was estimated; the data provided were insufficient to assess whether the approach could have introduced bias to the estimates derived. Given concerns with the potential biases introduced by the regression model, the CDR reanalysis used the reported change in utilities, from baseline to 16 weeks as observed in the LIBERTY AD CHRONOS trial within each treatment arm, to determine the utility values at week 16.[2,3]

Furthermore, the manufacturer's model took a treatment-specific approach to estimate and apply utility weights after week 16. In the dupilumab plus SOC arm, utility values were based on whether a patient responded to treatment, with a higher utility weight applied to responders (0.9029) compared with nonresponders (0.8175); whereas in the SOC arm, the utility values reflected the week 16 utility value estimated for all patients on SOC (0.8175).[2] As there is no justification for different approaches to model the utility values after 16 weeks of treatment, a CDR reanalysis was conducted in which identical methods were used to estimate and model utility for SOC after 16 weeks. At week 16, those on SOC were separated into responders (probability = 12.4%[2,3]) or nonresponders and, similarly, utility values were not only treatment-specific but also reflected responder status. The utility of responders on SOC was adjusted as follows:

> Utility of responders on SOC = utility of all patients on SOC at week 16 + (utility of responders on dupilumab at week 16 minus utility of all patients on dupilumab at week 16)
>
> Utility of nonresponders on SOC = (utility of all patients on SOC at week 16 minus utility of responders on SOC × probability of response on SOC at week 16) ÷ (1 minus probability of response on SOC at week 16)

4) **Durability of response beyond trial duration:** In the manufacturer's model, treatment-specific assumptions were made regarding the persistence of the treatment response.[2] For responders on SOC, treatment response would be lost at 52 weeks (i.e., treatment waning), as — regardless of responder status — all patients would return to their baseline utility value (0.6400), adjusted by age. The manufacturer justified this assumption based on feedback from their key opinion leaders that the effects of treatment on SOC last four to six weeks.[2] However, the clinical expert consulted as part of this review disagreed with this assumption, as it is expected that patients responding to SOC would have improved quality of life over those not responding to treatment. Furthermore, the LIBERTY AD CHRONOS trial reported that 45.4% of the all-observed SOC population would still meet the EASI-50 (50% or greater improvement in EASI from baseline) criteria at 52 weeks.[2] This suggests that not all patients should revert to the baseline utility at 52 weeks. The manufacturer assumed no waning effect for patients on dupilumab plus SOC.[2] Patients who responded at 16 weeks to dupilumab plus SOC were assumed to have a utility weight reflective of treatment responders (0.9029), adjusted by age, for the rest of their life unless treatment was discontinued. This does not align with the LIBERTY AD CHRONOS trial findings that reported a reduction in the proportion of responders for dupilumab plus SOC between week 16 and week 52 (proportion of responders defined

by EASI-50: 85.8% and 81.1% at week 16 and week 52 respectively; defined by EASI-75 (75% or greater improvement in EASI from baseline): 73.6% and 60.4% at week 16 and week 52, respectively).[2] The decline in effectiveness between 16 weeks and 52 weeks suggests that durability of treatment response continues to decline after 52 weeks. The manufacturer's approach underestimates the absolute benefit of SOC while it overestimates the absolute benefit of dupilumab plus SOC.

Current guidelines for the conduct of economic evaluations state that it is not acceptable to assume that the relative effectiveness will be maintained for the duration of the intervention.[6] No justification was provided to support the assumption of no treatment waning with dupilumab. According to the clinical expert consulted as part of this review, treatment waning is a realistic assumption. CDR's reanalysis was informed by the opinion of the clinical expert consulted as part of this review. The clinical expert did not agree that those who continue to respond to SOC at one year would have a utility value identical to nonresponders. However, the clinical expert did state that a high proportion of patients who respond to dupilumab and stay on treatment would maintain their improved quality of life, and stated that this would also be true for those responding to SOC. In the CDR reanalysis, it was assumed that the utility weight of both dupilumab and SOC responders would decrease over time, but at the same rate (i.e., that utility value for responders would return to the baseline utility after 40 years of treatment).

5) **Annual discontinuation estimates for dupilumab:** The manufacturer's submitted model applied a discontinuation rate of 2.4% to treatment responders starting from the second year of treatment, which was based on a discontinuation rate for responders of between 16 weeks and 52 weeks in the LIBERTY AD CHRONOS trial.[2,3] This meant that, among patients who proceeded to maintenance therapy, 11% would have discontinued use of dupilumab after five years. This value does not align with those reported in the literature, in which the discontinuation rate of biologics in patients with psoriasis at five years has been shown to range from 25% to 89%.[10] The manufacturer provided an alternative discontinuation rate for responders based on the findings from the SOLO trials (6.3%).[2,8,9] In the CDR reanalysis, an annual discontinuation rate of 6.3% would result in 28% of responders discontinuing after five years. Applying this rate better aligns with the discontinuation rate observed in patients with psoriasis on biologics.

6) **Full indication not addressed:** The economic analysis did not adequately assess the cost-effectiveness of dupilumab in patients in which topical prescription therapies are not advisable. The clinical expert consulted for the CDR review noted this is likely to represent a small portion of patients who would be receiving this treatment.

CADTH Common Drug Review Reanalyses

The results of the CDR reanalysis are reported in Table 3. The reanalysis addressed the limitations identified above by:

- assuming a 96.89% compliance rate for dupilumab, for consistency
- adjusting treatment-specific utility values to reflect the utility change observed in the CHRONOS trial (based on LOCF)
- incorporating identical assumptions pertaining to waning effects for dupilumab and SOC (utility weights decline at a linear rate over 40 years)
- adjusting long-term clinical benefits for responders on SOC

- revising the annual discontinuation rate for dupilumab of 2.4% to 6.3% in order to better align with a discontinuation rate reported in a similar clinical area

Compared with the manufacturer's results, the CDR reanalysis reported lower expected costs for SOC, but higher expected costs for dupilumab plus SOC, while QALYs for dupilumab plus SOC and SOC alone were higher than reported by the manufacturer's results. Under the CDR base case, the ICUR for dupilumab plus SOC was estimated to be $579,672 per QALY compared with SOC alone (Table 3).

Table 3: CDR Reanalysis of Limitations

	Scenario	Treatments	QALYs	Cost	ICUR (per QALY)
	Base case, submitted by manufacturer	SOC	21.06	$129,166	$89,890
		Dupilumab plus SOC	22.31	$241,528	
1	**Compliance**				
1a[a]	**96.89% compliance**	SOC	21.05	$129,173	$107,359
		Dupilumab plus SOC	22.29	$262,223	
2)	**Utilities**				
2a[a]	**Utility weight based on observed change from baseline from LIBERTY AD CHRONOS trial, LOCF**	SOC	21.19	$129,211	$140,326
		Dupilumab plus SOC	21.99	$240,879	
2b	**Utility weight based on observed change from baseline from LIBERTY AD CHRONOS trial, as observed**	SOC	21.22	$129,500	$142,151
		Dupilumab plus SOC	22.00	$241,258	
3	**Treatment waning**				
3a	**Waning of SOC: 2 years**	SOC	21.14	$129,385	$91,166
		Dupilumab plus SOC	22.37	$240,753	
3a	**Waning of SOC: 10 years**	SOC	21.81	$129,056	$101,608
		Dupilumab plus SOC	22.90	$240,022	
3b	**Waning of SOC: 40 years[a]**	SOC	23.83	$129,046	$142,166
		Dupilumab plus SOC	24.62	$240,957	
3c	**Waning of dupilumab: 2 years**	SOC	21.06	$129,568	$366,455
		Dupilumab plus SOC	21.12	$151,710	
3d	**Waning of dupilumab: 10 years**	SOC	21.05	$128,935	$199,277
		Dupilumab plus SOC	21.30	$178,684	
3e[a]	**Waning of dupilumab: 40 years**	SOC	21.05	$129,523	$145,552
		Dupilumab plus SOC	21.76	$233,053	
4	**Approach to model the long-term clinical benefit among patients responding to SOC (beyond 16 weeks)**				
4a	**2a + identical methods to estimate and model utility for SOC after 16 weeks + 2.4% annual discontinuation rate applied to both treatment arms**	SOC	21.22	$129,090	$143,599
		Dupilumab plus SOC	22.01	$241,959	
4b	**2b + identical methods to estimate and model utility for SOC after 16 weeks + 2.4% annual discontinuation rate applied to both treatment arms**	SOC	21.20	$128,724	$142,383
		Dupilumab plus SOC	21.98	$241,034	
4c[a]	**2b + identical methods to estimate and model utility for SOC after 16 weeks + 6.3% annual**	SOC	21.27	$125,580	$160,703
		Dupilumab plus SOC	21.99	$240,463	

	Scenario	Treatments	QALYs	Cost	ICUR (per QALY)
	discontinuation rate applied to both treatment arms				
4d	**2a + identical methods to estimate and model utility for SOC after 16 weeks + 6.3% annual discontinuation rate applied to both treatment arms**	SOC	21.32	$125,968	$169,186
		Dupilumab plus SOC	22.00	$241,460	
4e	**4f + responder defined based on EASI-50**	SOC	21.59	$87,301	$174,102
		Dupilumab plus SOC	23.10	$351,405	
5	**Discontinuation rate**				
5a[a]	**Annual discontinuation on dupilumab: 6.3% from SOLO trial**	SOC	21.06	$128,840	$89,664
		Dupilumab plus SOC	22.31	$241,260	
5b	**Annual discontinuation on dupilumab: based on the percentage of responders at week 16 who are nonresponders at week 52**	SOC	21.06	$129,012	$89,755
		Dupilumab plus SOC	22.30	$241,077	
6)	**CDR base-case reanalysis**	SOC	22.69	$126,708	$579,672
		Dupilumab plus SOC	22.90	$253,579	

CDR = CADTH Common Drug Review; EASI-50 = 50% or greater improvement in Eczema Area and Severity Index from baseline; ICUR = incremental cost-utility ratio; LOCF = last outcome carried forward; QALY = quality-adjusted life year; SOC = standard of care.
[a] Indicates scenarios included in the CDR base-case reanalysis.

A price-reduction analysis (Table 4) demonstrates that, in using the manufacturer's base-case analysis, dupilumab would be considered cost-effective at $50,000 per QALY at a 40% price reduction. Using the CDR reanalysis, dupilumab would be cost-effective at $50,000 per QALY following a price reduction of 84% and, in order to be cost-effective at $100,000 per QALY, a price reduction of 75% would be required.

Table 4: CDR Reanalysis Price Reduction Scenarios

ICURs of Dupilumab Plus SOC Versus SOC		
Price Reduction	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CDR (Based on CDR Base Case)**
Submitted	$90,845	$501,646
10%	$80,283	$447,276
20%	$69,721	$392,906
30%	$59,160	$338,536
40%	$48,598	$284,166
50%	$38,036	$229,797
60%	$27,474	$175,427
70%	$16,192	$121,057
80%	$6,350	$66,687
90%	Cost savings	$12,317

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; SOC = standard of care.

Note: All results are deterministic.

Issues for Consideration

- As noted by the CDR clinical expert, there is no clear and objective definition of response. The clinical expert stated that the EASI score is more likely to be used to define response to treatment.
- Although dupilumab is indicated for use as a second-line drug in the treatment of moderate-to-severe atopic dermatitis 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 drug, after failing systemic therapy or phototherapy.[11] There is, however, no comparative clinical effectiveness data between dupilumab plus SOC compared with these therapies, which would inform the potential cost-effectiveness of dupilumab when compared against these alternative therapies.

Patient Input

Input was received by one patient group, the Eczema Society of Canada (ESC). The ESC reported many consequences of atopic dermatitis that affect patients' quality of life, including: itching, pain, anxiety, depression, social isolation, productivity effects, poor self-esteem, and suicidal thoughts. Patients who participated in the clinical trial reported a reduction or elimination of flare-ups and itch. Their comments support the lower baseline utility value that was used in the model for moderate-to-severe atopic dermatitis. Although comments from patients who had experienced successful treatment with dupilumab suggest an improvement in quality of life compared with alternative treatments in terms of reducing disease severity, this was not adequately addressed in the manufacturer's submitted economic model; treatment efficacy was driven solely by the dichotomous outcome of treatment response rather than explicitly modelling change in disease severity. The ESC also reported that caregivers also suffer sleep loss, anxiety, and depression, although the

effects on the caregiver were not reported by the manufacturer or captured in the submitted economic model.

Conclusions

The key limitations were the assumptions on the sustained treatment effect of dupilumab plus SOC, the use of the regression analysis to estimate treatment-specific utility values, and the partial incorporation of the effects of poor compliance. The CDR reanalysis addressed the aforementioned limitations within the manufacturer's economic analysis. In patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies, the ICUR was estimated at $579,672 per QALY for dupilumab plus SOC compared with SOC alone.

The difference in incremental utilities was driven largely by the approach taken to model utilities and the assumptions around the waning of the treatment effect for both treatment arms in the model. The model was sensitive to both sets of assumptions.

A price reduction of 84% would be required for the ICUR of dupilumab plus SOC to fall below the $50,000 per QALY when compared with SOC alone. CDR was unable to assess the cost-effectiveness of dupilumab plus SOC compared with the alternative comparators that are presently used by patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies. The magnitude of clinical benefit that dupilumab may offer compared with these alternative treatments is uncertain, given the lack of comparative effectiveness evidence.

CADTH notes that this model does not explicitly address the population of patients for whom topical therapies are not advisable, and the ICUR is presently unknown in this patient population.

Appendix 1: Cost Comparison

The comparators presented in Table 5 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 Table 5 and, as such, may not represent the actual costs to public drug plans.

Table 5: CDR Cost Comparison Table of Systemic Treatments for Atopic Dermatitis in Adults

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Cost per Day ($)	Cost per Course ($)
Dupilumab (Dupixent)	**300 mg/ 2 mL**	**Pre-filled syringe**	**$1,153.8500[a]**	**600 mg as an initial dose followed by 300 mg every two weeks**	**82.42**	**First year: 31,154 Annual average thereafter: 30,000**
Alitretinoin (Toctino)[b]	10 mg 30 mg	Capsule	21.99	30 mg once daily; if unacceptable side effects, dosage may be reduced to 10 mg for 24 weeks	21.99	3,694
Other treatments not specifically indicated for the treatment of atopic dermatitis						
Acitretin (Soriatane)[b]	10 mg 25 mg	Capsule	2.5930 4.5540	10 mg to 50 mg once daily; maximum of 75 mg once daily for 24 weeks	2.59 to 9.11	436 to 1,530
Apremilast (Otezla)	10 mg 20 mg 30 mg	Tablet	19.5715[c]	30 mg twice daily, starting with titration pack (27-tablet kit titrating from 10 mg once daily to 30 mg twice daily)	39.14	14,287 annually
Ustekinumab (Stelara)	45 mg 90 mg	Pre-filled syringe	4,593.1400	45 mg SC at weeks 0 and 4 and then every 12 weeks thereafter; 90 mg may be used for patients weighing more than 100 kg	54.68	First year: 22,966 Annual average thereafter: 19,958
Immunosuppressants						
Azathioprine (generic)	50 mg	Tablet	0.2405	1.5 mg/kg/day to 2.5 mg/kg/day for 24 weeks	0.48 to 0.96[d]	80 to 162
Cyclosporine (generic)	10 mg 25 mg 50 mg 100 mg	Capsule	0.6238 0.9952 1.9400 3.8815	2.5 mg/kg to 5 mg/kg per day in two divided doses for 24 weeks	7.76 to 13.58[d]	1,304 to 2,281
Methotrexate (generic)	2.5 mg	Tablet	0.6235	10 mg/week to 22.5 mg/week for 24 weeks	2.49 to 5.61 per week	60 to 135
Mycophenolate mofetil	250 mg 500 mg	Capsule	0.5155 1.0310	1 g twice daily for first 4 weeks; 1.5 mg daily for 20 weeks	First 4 weeks: 4.12 Thereafter: 3.09	548

CDR = CADTH Common Drug Review; SC = subcutaneous.

[a] Manufacturer's submitted price.

[b] According to the CDR clinical expert consulted for this review, retinoids are primarily used to treat hand dermatitis.

[c] IQVIA DeltaPA[13] wholesale price (retrieved December 12, 2017).

[d] Assumes patient weight of 70 kg.

Source: Ontario Drug Benefit Formulary list prices[12] unless otherwise indicated; recommended doses from respective product monographs unless otherwise indicated.

In addition, according to the clinical expert consulted as part of this review, the following topical treatments and phototherapy may be used to treat moderate-to-severe atopic dermatitis despite not being indicated (Table 6).

Table 6: CDR Cost Comparison Table of Topical Treatments for Atopic Dermatitis in Adults

Drug/Comparator	Strength	Dosage Form	Price per Gram ($)	Recommended Dose
Topical corticosteroids				
Amcinonide (generics)	0.1%	Cream Lotion Ointment	0.1955 0.2600 0.2500	Thin amount applied to affected area twice daily for a maximum of 5 days on the face, axillae, scrotum, or scalp, and two to three weeks elsewhere.
Betamethasone dipropionate (generic)	0.05%	Cream Lotion Ointment	0.2048 0.1980 0.2152	Thin film applied to affected area twice daily. Duration of therapy varies. Need should be reassessed at least every 4 weeks.
Betamethasone valerate (generic)	0.1%	Cream Lotion Ointment	0.0889 0.3125 0.0889	No recommended daily dose. Use as directed by clinicians.
Clobetasol propionate (generic)	0.05%	Cream Scalp Lotion Ointment	0.2279 0.1990 0.2279	Thin amount applied to affected area twice daily. Weekly application should not exceed 50 g and should be limited to two consecutive weeks.
Desonide (generic)	0.05%	Cream Ointment	0.2650 0.2647	Thin amount applied to affected area twice daily. May be increased in refractory cases.
Desoximetasone (Topicort)	0.25%	Cream Ointment	0.6985[a] 0.6604[a]	Thin amount applied to affected area twice daily.
Fluocinonide (Lyderm, Lidex)	0.05%	Cream Emollient Cream Gel Ointment	0.2378 0.1980 0.3076 0.3035	Thin amount applied to affected area twice daily. Weekly application should not exceed 45 g and should be limited to two weeks.
Halobetasol propionate (Ultravate)	0.05%	Cream Ointment	1.0292[b] 0.9996[b]	Thin amount applied to affected area twice daily, limited to 50 g weekly for no more than two weeks without re-evaluation.
Hydrocortisone (various)	1.0% 2.5%	Cream	0.1718 0.2014	No recommended daily dose. Use as directed by clinicians.
	1.0% 2.5%	Lotion	0.1587 0.2100	
	0.5% 1.0%	Ointment	0.1333 0.0390	
Hydrocortisone valerate (Hydroval)	0.2%	Cream Ointment	0.1313	Small amount applied to affected area twice daily. Discontinue as soon as lesions heal or if no response.
Mometasone furoate (generic)	0.1%	Cream Lotion Ointment	0.5263 0.3358 0.2252	Thin film applied to affected areas twice daily.
Triamcinolone acetonide (various)	0.1%	Cream	0.0562	No recommended daily dose. Use as directed by clinicians.
Topical calcineurin inhibitors				
Pimecrolimus (Elidel)	1%	Cream	2.3220	Thin layer applied to affected area twice daily. Discontinue when resolved or after three weeks if no improvement or exacerbation.

Drug/Comparator	Strength	Dosage Form	Price per Gram ($)	Recommended Dose
Tacrolimus	0.03% 0.10%	Cream	2.2145 2.3690	Thin layer applied to affected area twice daily. Discontinue after six weeks if no improvement or exacerbation.
Phototherapy				
Ultraviolet light therapy	NA	NA	7.85 per treatment[c]	Three times weekly, for 24 weeks.

CDR = CADTH Common Drug Review; NA = not applicable.

[a] Saskatchewan Formulary list price[14] (December 2017).
[b] British Columbia Formulary list price, as reported by IQVIA DeltaPA[13] (December 2017).
[c] Ontario Schedule of Benefits for Physician Services, code G470 (Ultraviolet Light Therapy), accessed December 2017.[15]

Source: Ontario Drug Benefit Formulary list prices[12] unless otherwise indicated. Recommended doses from respective product monographs unless otherwise indicated.

Appendix 2: Summary of Key Outcomes

Table 7: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive is Dupilumab Plus Standard of Care Relative to the Standard of Care?

DUPILUMAB Plus SOC Versus SOC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug-treatment costs alone					X	
Clinical outcomes	X					
Quality of life		X				
Incremental CE ratio (CDR reanalysis)	Manufacturer's base case: $89,723[a] per QALY CDR base case: $579,672 per QALY					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; SOC = standard of care.

[a] Not reported but calculated from manufacturer model.

Appendix 3: Additional Information

Table 8: 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”	A number of model assumptions remain unjustified. For example: Why were different response utilities used between treatment arms contrary to current guidelines to economic modelling, or why it was assumed that the quality of life of responders on dupilumab did not decrease over time? In addition, there were certain details pertaining to treatment efficacy and continuation described in the pharmacoeconomic report and accompanied model that did not align with the clinical data provided by the manufacturer.		
Was the material included (content) sufficient?		X	
Comments Reviewer to provide comments if checking “poor”	Although insufficient detail was provided to be assured that the health-related quality of life regression analysis was unbiased, the model was flexible to permit reanalyses that explored alternative approaches to derive the treatment-specific utility weights.		
Was the submission well organized and was information easy to locate?	X		
Comments Reviewer to provide comments if checking “poor”	None		

Table 9: Authors’ 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 over the methods and right to publish analysis			X

Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

No other health technology assessment agencies have reviewed dupilumab for the requested CADTH Common Drug Review indication**.** It is currently undergoing review by the National Institute for Health and Care Excellence (NICE) (invitation to participate posted on October 7, 2018). Dupilumab was previously reviewed by NICE in 2004 for the indication of atopic eczema.[16]

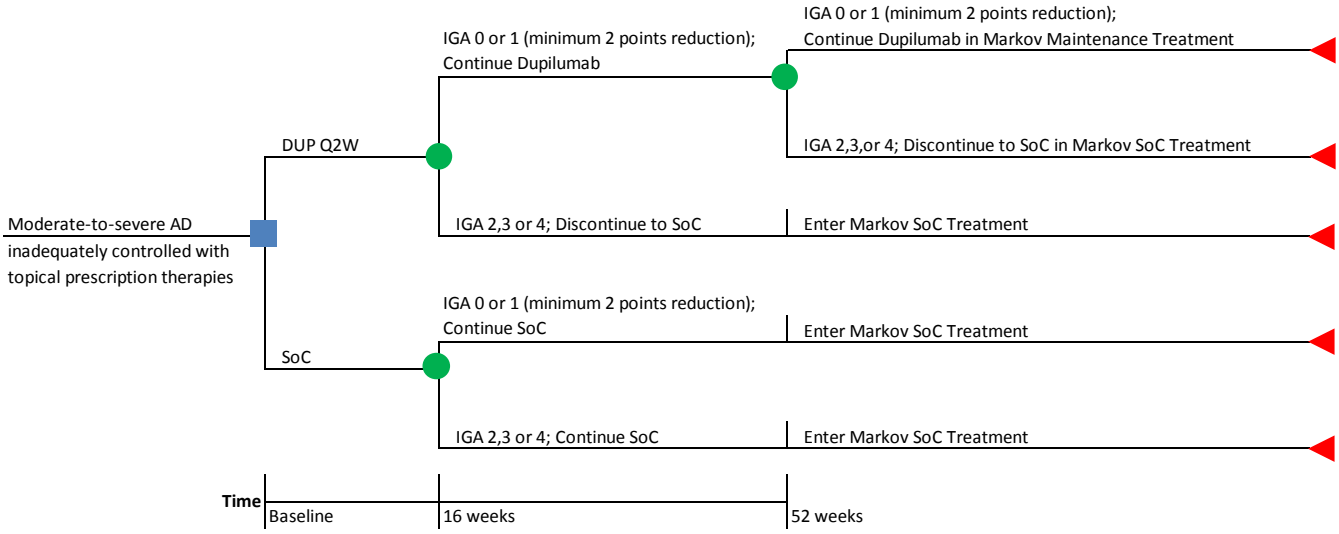
Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer submitted a hybrid model that considered a lifetime horizon (64 years) in a patient cohort with an average age of 37.6 years, 58.7% males with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies.[2] The model consisted of a short-term decision tree that reflected the first year of treatment and a long-term cohort state transition model reflecting the patient's lifetime after the first year of treatment.[2] The decision tree was based on response, defined as those who do not use a systemic immunosuppressant (such as methotrexate) and achieve an Investigator's Global Assessment (IGA) end point of 0 or 1 with a reduction from baseline of greater than or equal to two points. The decision tree estimated the expected costs and quality-adjusted life-years (QALYs) during the 16-week and 52-week trial period, after which patients were modelled by a cohort state transition model with annual cycles that were based on three health states: on dupilumab, on SOC, or death.[2] The short-term decision tree and long-term state transition model structure, as presented by the manufacturer, can be seen in Figure 1 and Figure 2, respectively.

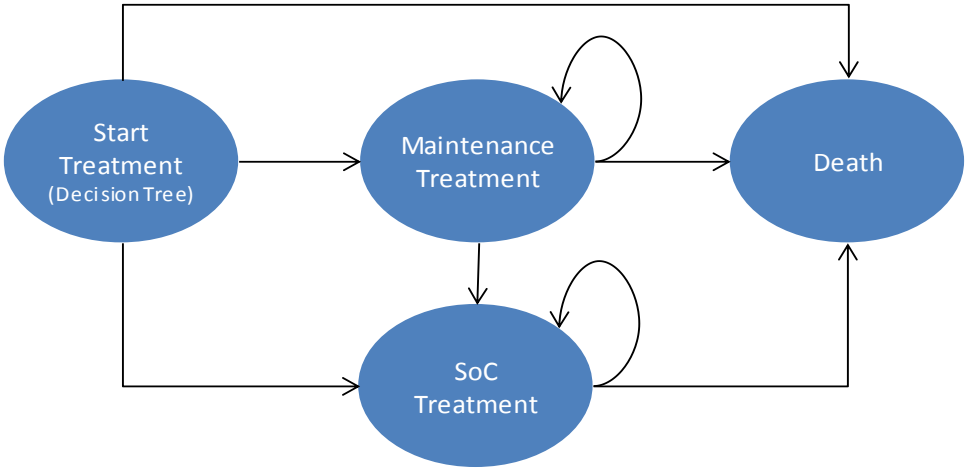
All patients entered the model as a nonresponder and, at 16 weeks, patients were assessed for response.[2] To adjust for the unknown time at which responders at 16 weeks actually responded, it was assumed that patients who responded at 16 weeks would have a higher utility at 8 weeks. In the dupilumab plus SOC arm, those who responded remained on dupilumab until 52 weeks, after which, nonresponders discontinued dupilumab and entered the "on SOC" health state, while responders remained on dupilumab and entered the "on dupilumab" health state of the Markov model.[2] In the long-term maintenance phase, patients may discontinue dupilumab and transition to SOC. In the SOC arm, it was assumed that no patients would respond past 16 weeks and that all patients — regardless of their treatment responder status — would enter the "on SOC" health state of the Markov model after 52 weeks.[2]

Figure 1: Short-Term Decision Tree Structure



AD = atopic dermatitis; DUP = dupilumab; IGA = Investigator's Global Assessment; Q2W = once every two weeks; SoC = standard of care.
Source: Manufacturer's pharmacoeconomic submission.[2]

Figure 2: Cohort State Transition Model Structure



SoC = standard of care.
Source: Manufacturer's Pharmacoeconomic Submission.[2]

The manufacturer used the findings reported in the LIBERTY AD CHRONOS trial[3] to inform the treatment-specific parameters on efficacy (i.e., probability of patients achieving response), safety (i.e., adverse events), and utilities. Of note, the manufacturer developed a mixed-model regression analysis based on forward-selection process to calculate treatment-specific utility weights.[2] In addition, the LIBERTY AD CHRONOS trial also informed parameters on discontinuation and compliance to dupilumab.[3] The model assumed treatment waning on the SOC arm, tapering utility values of responders back to baseline trial values after 52 weeks, while responders to dupilumab were not affected by treatment waning. The manufacturer's model assumed no mortality effect with treatment and baseline mortality, and was based on the life tables of the Canadian general population.[2]

Table 10: Data Sources

Data Input	Description of Data Source	Comment
Efficacy	[redacted] and achieved an IGA end point of 0 or 1 with a reduction from baseline of greater than or equal to two points. The probability of response at 16 weeks and 52 weeks was taken from the LIBERTY AD CHRONOS trial. Assumptions on treatment waning for SOC were based on expert opinion. No justification was provided on the assumption that dupilumab had no treatment waning.	It was unclear how the probability of response at 52 weeks was calculated. These numbers do not align with the clinical data submitted by the manufacturer. The assumption of treatment waning for SOC was based on the opinion of clinical experts who suggested the duration of efficacy of SOC, when treating patients with AD, is four to six weeks. This, however, does not align with the clinical trials' findings, which observed that 6.8% of patients would still be defined as responders using the IGA criteria, while 45.4% of patients would still be classified as responders using the EASI-50 definition. Treatment waning on dupilumab is unknown, given the lack of long-term evidence. Feedback from the clinical expert consulted by CDR suggests that both treatments were likely to decrease in efficacy over time. There is no clear rationale provided to support the assumption that poor compliance to dupilumab would not affect treatment response. This assumption is not appropriate.

Data Input	Description of Data Source	Comment
	Lack of compliance to dupilumab was assumed to not have an impact on treatment efficacy.	
Natural history	Discontinuation at 52 weeks was estimated for those who responded at 16 weeks in the LIBERTY AD CHRONOS trial.[3]	The manufacturer used the rate of non-completers in the 52-week treatment period from the LIBERTY AD CHRONOS trial (2.4%).[3] This meant that, in the manufacturer's base-case analysis, 11% of patients who remained on treatment after the first year of treatment would have discontinued use of dupilumab five years later. It was, however, unclear how the probabilities for treatment discontinuation were derived, as these numbers do not align with the clinical data submitted by the manufacturer. Trial discontinuation is likely to be lower than real-world discontinuation. Discontinuation of biologics in patients with psoriasis at 5 years has been shown to range from 25% to 89%.[3] Within the clinical trial program for dupilumab, combining SOLO 1 and 2 trial data, discontinuation rates at 52 weeks were reported to be 6.3%.[8,9]
Utilities	Treatment-specific utilities were obtained from a mixed-model regression analysis with forward selection to determine regression covariates.[2] Regression was based on EQ-5D data, with LOCF imputation methods, based on the data from the LIBERTY AD CHRONOS trial.[3]	It is recommended that health-state utilities be used for health technology assessment rather than treatment-specific utilities.[6] The choice of treatment-specific utilities was not well justified by the manufacturer. Furthermore, the regression model was not well explained or justified, including how covariates were selected, despite a request to the manufacturer for additional information, which was responded to. The forward-selection process resulted in the following regression covariates: age, male, baseline EQ-5D, total EASI score, weekly average of peak daily pruritus, EASI–pruritus interaction, and a treatment dummy. However, it was unclear why other covariates such as DLQI were not tested. The use of the regression approach to elicit utilities had larger differences between treatments than the observed trial utility difference between treatments. The treatment-specific utility weight of 0.9029 for dupilumab plus SOC and 0.8175 for SOC alone can be interpreted as patients being willing to trade off 31 days of life each year to have a response on dupilumab plus SOC over SOC. It is unclear why different approaches were used to determine the utility weights at different time points in the model. For instance, all patients begin the model with the average baseline utility weight reported in the LIBERTY AD CHRONOS trial (0.64). Among responders in the first 16 weeks, treatment-specific utility weights based on the regression model using data on all patients from the LIBERTY AD CHRONOS trial were employed (dupilumab plus SOC: 0.8898; SOC: 0.8175). After 16 weeks, patients in the dupilumab plus SOC arm who remained responders were assigned the utility weight of the week 16 responders from the LIBERTY AD CHRONOS trial (0.9029), whereas patients on SOC after week 16 continued to have the same utility weight as all patients assessed at week 16 (0.8175) until the first year when treatment waning resulted in all patients being assigned the average baseline value (0.64). This approach meant that, under the lifetime horizon, patients would be willing to give up approximately 5.5 years of perfect life to have the utility weight of dupilumab over their lifetime. There were no utility decrements associated with adverse events.

Data Input	Description of Data Source	Comment
Resource use	Resource use, based on responder status, was informed by the AWARE study.[5] Drug utilization was based on the dosing regimen specified in the product monograph,[1] adjusted for compliance using the real-world compliance rate for biologics in moderate-to-severe psoriasis patients in Canada.	The AWARE study combined patients from France, Germany, Italy, the UK, Spain, and Canada. Resource use was based on patients' responses. Resources used by responders included visits to health care providers and UV treatment or phototherapy. Resource use captured for nonresponders included visits to health care providers, UV treatment or phototherapy, hospitalization, and other biologic use besides dupilumab. Compliance lowers drug use. Although this may be appropriate to provide more realistic estimates on drug-specific costs, in the context that compliance did not impact treatment efficacy (i.e., responders or discontinuation rates), this approach would systematically reduce the cost-effectiveness of dupilumab.
Adverse events (indicate which specific adverse events were considered in the model)	Adverse event rates are from the LIBERTY AD CHRONOS trial[3] and included injection-site reaction, allergic conjunctivitis, infectious conjunctivitis, and oral herpes.	Adverse events have no additional effect on the patient's quality of life except for that which is captured in the treatment-specific HRQoL.
Mortality	Canadian life tables.	Appropriate. No increase in mortality is assumed for patients with uncontrolled AD.
Health state–specific costs	AWARE study and claims data study.[4,5]	The manufacturer took a macro approach based on responder status. The annual cost for a responder was estimated to be $173 (based on the mild AD population in the AWARE study), while the annual costs of nonresponders was estimated to be $4,193. Responder costs include health care provider costs and UV treatment or phototherapy. Nonresponder costs include responder costs plus hospitalization and other biologic use, beside dupilumab. The highest cost beside dupilumab is for other biologic treatments ($2,647.93).
Drug costs	Cost of dupilumab provided by the manufacturer. Costs of mid-potency topical corticosteroids and topical calcineurin inhibitors were not included separately.	Unit cost is appropriate. Given that both arms included mid-potency topical corticosteroids or topical calcineurin inhibitors, these drug costs were not included in the model. If the use of dupilumab reduces the use of topical treatments, this may be a conservative assumption.
Administration costs	Not included.	The manufacturer assumed that the administration cost (specifically, the cost of training patients on administering subcutaneous injections) would be covered by the manufacturer through a patient support program and was not included in the model.
Costs of managing adverse events	Ontario Schedule of Benefits.[15]	Costs of each adverse event are assumed equal to a minor assessment from a physician, costing $21.70. Not appropriate, but unlikely to impact the results.
Health state	Decision tree based on responder status. Three health states in the Markov model: (responder) on dupilumab, on SOC, and dead.[2]	The health states in the Markov model were treatment-specific. Modelling guidelines recommend that models use health states based on the patient's health and not on treatment-specific health states.

AD = atopic dermatitis; CDR = CADTH Common Drug Review; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI-50 = 50% or greater improvement in EASI from baseline; EQ-5D = EuroQol 5-Dimensions questionnaire; HRQoL = health-related quality of life; ICUR = incremental cost-utility ratio; IGA = Investigator's Global Assessment; LOCF = last observation carried forward; SOC = standard of care; UV = ultraviolet.

Table 11: Manufacturer's Key Assumptions

Assumption	Comment
Responders to dupilumab have continued effect until they discontinue.	This assumption was tested by CDR and found to be very influential to the ICUR. This was not considered reasonable by CDR.
Patients who respond have different HRQoL, depending on their treatment.	Although this is contrary to modelling guidelines, this may be justifiable, given that not all responders are the same. Within the clinical trials, there was a difference observed in terms of the proportion of patients achieving EASI-50 and EASI-75 within each arm.
No increase in mortality is assumed for patients with uncontrolled atopic dermatitis.	No evidence was presented to suggest a difference in mortality rates between treatments, and this assumption was considered reasonable by the CDR.
Patient characteristics: 58.7% male, aged 37.6 years.[2]	The base-case patient population for the model is based on the patient population in the LIBERTY AD CHRONOS trial and was considered reasonable by CDR.
Patients are 81.7% compliant to dupilumab, which decreases the costs of dupilumab, but not the effectiveness.	This assumption was tested by CDR and found to be influential to the ICUR. This assumption was not considered reasonable by CDR.
No cost for self-administration.	The manufacturer assumed that the administration cost, specifically, the cost of training patients to administer subcutaneous injections, would be covered by the manufacturer through a patient support program.
Efficacy of treatment applied at 8 weeks.	It was assumed that responders at 16 weeks would achieve improved quality of life 8 weeks into treatment. Noting that patients will achieve a response at different points prior to the 16-week measurement of response, this approach selected the mean time point at which to apply the treatment benefits. CDR considered this assumption to be reasonable.
Treatment waning of SOC after 1 year, but no treatment waning of dupilumab.	Current guidelines for the conduct of economic evaluations state that it is not acceptable to assume that the relative effectiveness will be maintained for the duration of the intervention. No justification was provided to support the assumption that dupilumab would have no treatment waning. According to the clinical expert consulted as part of this review, treatment waning is a realistic assumption. The clinical expert stated that a high proportion of patients who respond to dupilumab and stay on treatment would maintain their improved HRQoL, and that this would also be true for the comparator. Given the lack of evidence to indicate a difference in treatment waning for responders to treatment, CDR did not consider a difference in waning to be a reasonable assumption.
Patients do not use immunosuppressants.	No comparison was made to the immunosuppressants that are commonly prescribed in this population. This was not considered reasonable by CDR.

CDR = CADTH Common Drug Review; EASI = Eczema Area and Severity Index; EASI-50 = 50% or greater improvement in EASI from baseline; EASI-75 = 75% or greater improvement in EASI from baseline; HRQoL = health-related quality of life; ICUR = incremental cost-utility ratio; SOC = standard of care.

Additional CADTH Common Drug Review Reanalyses

The primary CDR reanalyses are presented in the main body of the report. Background information on the definition of response and utility weight estimation is provided subsequently.

Response: The primary measures of response excluded the use of systemic immunosuppressants, meaning that if systemic immunosuppressants were used by the patient, they were considered to be a nonresponder whether or not they qualified as a nonresponder by the measure being used. This biases the results against SOC since systemic immunosuppressants are a part of SOC. This assumption is optimistic for the manufacturer and decreases the incremental cost-utility ratio. This was tested by CDR and not considered to be a key limitation.

Table 13: Response Reported by the Manufacturer for Different Measures

Scenario	Response Time Point	Dupilumab	SOC
Base-case analysis submitted by manufacturer	16 weeks	38.7%	12.4%
	52 weeks	20.8%	6.8%
EASI-50, primary analysis	16 weeks	38.7%	15.6%
	52 weeks	20.8%	8.6%
EASI-50, all observed	16 weeks	80.2%	37.5%
	52 weeks	75.8%	30.4%
EASI-75, primary analysis	16 weeks	85.8%	55.9%
	52 weeks	81.1%	45.4%
EASI-75, all observed	16 weeks	68.9%	23.2%
	52 weeks	56.5%	16.4%

EASI = Eczema Area and Severity Index; EASI-50 = 50% or greater improvement in EASI from baseline; EASI-75 = 75% or greater improvement in EASI from baseline; SOC = standard of care.
Note: All observed = all patients achieving the response criteria, regardless of immunosuppressant use.

Based on feedback from the clinical expert consulted for this review, physicians are more familiar with Eczema Area and Severity Index (EASI) scores and more likely to use them in clinical practice. Additionally, the definition of primary response used by the manufacturer excludes the use of immunosuppressants but, because immunosuppressants are part of the SOC in Canada, this definition decreases the response of the SOC arm. CDR conducted a reanalysis using the EASI scores to define response and allowing the use of immunosuppressants. This was tested by CDR and not considered to be a key limitation.

Table 14: Further CDR Reanalysis of Response

Scenario	Treatments	QALYs	Cost	ICUR (per QALY)
Base-case analysis submitted by manufacturer	Standard of care	21.06	$129,166	
	Dupilumab	22.31	$241,528	$89,890
EASI-50, primary analysis	Standard of care	21.05	$97,336	
	Dupilumab	23.85	$350,776	$90,750
EASI-75, primary analysis	Standard of care	21.06	$115,861	
	Dupilumab	23.30	$314,087	$88,495
EASI-50, all observed	Standard of care	21.05	$79,266	
	Dupilumab	24.05	$354,754	$92,361
EASI-75, all observed	Standard of care	21.05	$107,758	
	Dupilumab	23.43	$319,642	$89,228

EASI = Eczema Area and Severity Index; EASI-50 = 50% or greater improvement in EASI from baseline; EASI-75 = 75% or greater improvement in EASI from baseline; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-years.
Note: All observed = all patients achieving the response criteria regardless of immunosuppressant use.

References

1. Dupixent (dupilumab): solution for subcutaneous injection 150 mg/mL [draft] [product monograph]. Mississauga (ON): Sanofi Genzyme; 2016 Dec 13.
2. Pharmacoeconomic evaluation. In: CDR submission: Dupixent (dupilumab), solution for subcutaneous injection (150 mg/mL). Company: Sanofi Genzyme [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Sanofi Genzyme; 2017 Oct 26.
3. Clinical Study Report:R668-AD-1224. A randomized, double-blind, placebo-controlled study to demonstrate the efficacy and long-term safety of dupilumab in adult patients with moderate-to-severe atopic dermatitis [**CONFIDENTIAL** internal manufacturer's report]. Tarrytown (NY): Regeneron Pharmaceuticals, Inc.; 2016 Jul 17.
4. Atopic dermatitis - lines of therapy. Understanding the atopic dermatitis patient profile through product usage and therapy progression. In: CDR submission: Dupixent (dupilumab), solution for subcutaneous injection (150 mg/mL). Company: Sanofi Genzyme [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Sanofi Genzyme; 2017 Oct 26. Mississauga (ON): Sanofi Genzyme; 2017.
5. Estimating the burden of illness in adult atopic dermatitis patients in France, Germany, Italy, Spain, UK and Canada. In: CDR submission: Dupixent (dupilumab), solution for subcutaneous injection (150 mg/mL). Company: Sanofi Genzyme [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Sanofi Genzyme; 2017 Oct 26. Mississauga (ON): Sanofi Genzyme; 2017.
6. Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada [Internet]. 4th ed. Ottawa: CADTH; 2006 Mar. [cited 2018 Feb 6]. Available from: https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf
7. Ortiz de Frutos FJ, Torrelo A, de LR, Gonzalez MA, Alomar A, Vera A, et al. Patient perspectives on triggers, adherence to medical recommendations, and disease control in atopic dermatitis: the DATOP study. Actas Dermosifiliogr. 2014 Jun;105(5):487-96.
8. Clinical Study Report:R668-AD-1334. A phase 3 confirmatory study investigating the efficacy and safety of dupilumab monotherapy administered to adult patients with moderate to severe atopic dermatitis [**CONFIDENTIAL** internal manufacturer's report]. Tarrytown (NY): Regeneron Pharmaceuticals, Inc.; 2016 Jun 30.
9. Clinical Study Report:R668-AD-1416. A phase 3 confirmatory study investigating the efficacy and safety of dupilumab monotherapy administered to adult patients with moderate to severe atopic dermatitis [**CONFIDENTIAL** internal manufacturer's report]. Tarrytown (NY): Regeneron Pharmaceuticals, Inc.; 2016 Jun 30.
10. Arnold T, Schaarschmidt ML, Herr R, Fischer JE, Goerdt S, Peitsch WK. Drug survival rates and reasons for drug discontinuation in psoriasis. J Dtsch Dermatol Ges. 2016 Nov;14(11):1089-99.
11. Atopic dermatitis: Recommendations for the use of systemic immunomodulatory agents [Internet]. Schaumburg (IL): American Academy of Dermatology; 2017. [cited 2017 Dec 4]. Available from: https://www.aad.org/practicecenter/quality/clinical-guidelines/atopic-dermatitis/phototherapy-and-systemic-agents/recommendations-for-systemic-immunomodulatory-agents
12. Ontario Ministry of Health and Long-Term Care. Ontario drug benefit formulary/comparative drug index [Internet]. Toronto: The Ministry; 2016. [cited 2017 Dec 12]. Available from: https://www.formulary.health.gov.on.ca/formulary/
13. DeltaPA [database on Internet]. Ottawa: IQVIA; 2017 [cited 2017 Dec 12]. Available from: http://www.imsbrogancapabilities.com/en/market-insights/delta-pa.html Subscription required.
14. Drug Plan and Extended Benefits Branch. Saskatchewan online formulary database [Internet]. Regina: Government of Saskatchewan; 2016. [cited 2017 Dec 12]. Available from: http://formulary.drugplan.ehealthsask.ca/
15. Ontario Ministry of Health and Long-Term Care. Schedule of benefits for physician services under the Health Insurance Act: effective December 21, 2015 [Internet]. Toronto: The Ministry; 2015. [cited 2017 Dec 12]. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/physserv_mn.html
16. Dupilumab for treating moderate to severe atopic dermatitis after topical treatments [Internet]. London: NICE; 2018. [cited 2018 Feb 6]. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10218 In development [GID-TA10218].