CADTH

CADTH COMMON DRUG REVIEW

# CADTH Canadian Drug Expert Committee Recommendation

(Final)

This recommendation supersedes the CADTH Canadian Drug Expert Committee recommendation for this drug and indication dated June 27, 2018.

**DUPILUMAB (DUPIXENT — SANOFI-AVENTIS CANADA INC.)**
Indication: Atopic dermatitis

**RECOMMENDATION**
The CADTH Canadian Drug Expert Committee recommends that dupilumab should be reimbursed for the treatment of atopic dermatitis only if the following conditions are met.

**Conditions for Reimbursement**
**Initiation criteria**
1. 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.
2. Patients must have had an adequate trial or be ineligible for each of the following therapies: phototherapy (where available), methotrexate, and cyclosporine.
3. Patients who have had an adequate trial phototherapy, methotrexate, and/or cyclosporine must have documented refractory disease or intolerance.
4. The physician must provide the Eczema Area and Severity Index (EASI) score and Physician Global Assessment score at the time of initial request for reimbursement.
5. The maximum duration of initial authorization is six months.

**Renewal criteria**
1. The physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as a 75% or greater improvement from baseline in the EASI score (EASI-75) six months after treatment initiation.
2. The physician must provide proof of maintenance of EASI-75 response from baseline every six months for subsequent authorizations.

**Prescribing conditions**
1. The patient must be under the care of a dermatologist.
2. Dupilumab is not to be used in combination with phototherapy or immunosuppressant drugs, such as methotrexate or cyclosporine.

**Pricing conditions**
Reduction in price.


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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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CADTH

# DUPILUMAB (DUPIXENT — SANOFI-AVENTIS CANADA INC.)

## Indication: Atopic dermatitis

This recommendation supersedes the CADTH Canadian Drug Expert Committee recommendation for this drug and indication dated June 27, 2018.

## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that dupilumab should be reimbursed for the treatment of atopic dermatitis (AD) only if the following conditions are met.

## Conditions for Reimbursement

**Initiation criteria**

1. 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.
2. Patients must have had an adequate trial or be ineligible for each of the following therapies: phototherapy (where available), methotrexate, and cyclosporine.
3. Patients who have had an adequate trial phototherapy, methotrexate, and/or cyclosporine must have documented refractory disease or intolerance.
4. The physician must provide the Eczema Area and Severity Index (EASI) score and Physician Global Assessment score at the time of initial request for reimbursement.
5. The maximum duration of initial authorization is six months.

**Renewal criteria**

1. The physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as a 75% or greater improvement from baseline in the EASI score (EASI-75) six months after treatment initiation.
2. The physician must provide proof of maintenance of EASI-75 response from baseline every six months for subsequent authorizations.

**Prescribing conditions**

1. The patient must be under the care of a dermatologist.
2. Dupilumab is not to be used in combination with phototherapy or immunosuppressant drugs, such as methotrexate or cyclosporine.

**Pricing conditions**

Reduction in price.

## Reasons for the Recommendation

1. Dupilumab demonstrated superiority in improving signs and symptoms of AD, as well as health-related quality of life, when compared with placebo in adolescents (one randomized controlled trial [RCT]), and in adults there were five RCTs) who had moderate-to-severe AD. Patients studied were those with an inadequate response to topical therapies or topical therapies were not advisable (one RCT based on the adolescent population and four RCTs based on the adult population), and where cyclosporine treatment was inadequate, associated with toxicities, or not recommended due to contraindications (1 adult RCT).
2. CDEC discussed patient and clinician input that AD is associated with intense symptoms (namely itching and pain) that can lead to sleep disruption, anxiety and depression, social isolation, and impaired quality of life. There are few treatment options after topical therapies and immunosuppressants have failed to improve symptoms. There is limited access to phototherapy across

Canada, particularly for patients living in rural areas. CDEC considered that dupilumab would provide a treatment option for patients who have not achieved desired outcomes with adequate trials of topical therapies, phototherapy (where available), and immunosuppressants, or for patients who are ineligible for these therapies or experienced toxicities.

3. At the sponsor–submitted price for dupilumab of $959.94 for each of the 200 mg and 300 mg injections, the incremental cost-effectiveness ratio (ICER) for dupilumab plus standard of care (SOC) versus SOC alone (topical therapy) was estimated in CADTH's reanalysis to be $136,025 per additional quality-adjusted life-year (QALY) gained in the Health Canada–indicated population. CADTH reported results of a scenario analysis on the reimbursement request population (patients within the Health Canada indication who were refractory to or ineligible for, systemic immunosuppressant therapies), the estimated ICER was similar ($133,000 per QALY). In an additional scenario analysis that considered the EASI-75 outcome for treatment response for the Health Canada–indicated population, the ICER was $120,758 per QALY.

## Implementation Considerations

1. Based on the trials, moderate-to-severe AD is defined as an EASI score of 16 points or higher, or an Investigator (Physician) Global Assessment score of three or four.
2. Adequate control and refractory disease are optimally defined using similar criteria to those used in the dupilumab RCTs, such as achieving an EASI-75.
3. Phototherapy may not be available in all jurisdictions. Geographic inability to access phototherapy should not preclude patients from accessing dupilumab if otherwise indicated.

## Discussion Points

- CDEC noted that, overall, the trial results were generalizable to the Canadian population with moderate-to-severe AD. However, patients who were using topical calcineurin inhibitors or topical corticosteroids, standard treatments for AD, within one to two weeks of the baseline visit were excluded from Study 1526, SOLO 1, SOLO 2, and LIBERTY AD CHRONOS, while the LIBERTY AD CAFÉ trial excluded patients who used topical calcineurin inhibitors within one week of the screening visit.
- CDEC noted that AD is a chronic, relapsing condition where patients often experience episodes of worsening symptoms throughout their lives. The included trials were limited to 16 weeks' (four trials) and 52 weeks' (one trial) duration. SOLO CONTINUE extended the duration of follow-up with a select population of patients from the SOLO trials by 36 weeks. Study 1343 (N = 275) and Study 1225 (N = 1,491) were single-group, open-label extension studies to assess the long-term safety of dupilumab in pediatric and adult patients with AD, respectively. Both studies are ongoing and added a median overall treatment exposure of 16 weeks (range 4.0 to 120.1) and 24 weeks (range 1.0 to 125.0), respectively. There are no safety data for dupilumab beyond one year of treatment, and therefore, the longer-term safety of dupilumab beyond one year is unknown.
- No evidence was available comparing dupilumab with other drugs commonly used in the treatment of AD. All of the RCTs compared dupilumab with placebo. Hence, the magnitude of clinical benefit with dupilumab compared with existing alternative treatments is unknown and there is insufficient evidence to make recommendations for placing dupilumab ahead of topical therapies, phototherapy, and commonly used immunosuppressants, such as methotrexate and cyclosporine.
- AD is a common condition with an estimated lifetime prevalence of 17% in the Canadian population, and there is evidence to suggest that the prevalence has increased over the past 30 years. The cost of treatment with dupilumab is higher than other available treatments and therefore the potential budget impact of dupilumab given the population size could be important.
- Dupilumab is unlikely to be cost-effective at the submitted price. A price reduction of at least 54% is required to improve its cost-effectiveness, relative to SOC, in the Health Canada–indicated and sponsor requested reimbursement populations, and generate an ICER that is less than $50,000 per QALY. A price reduction analysis on the population aligned with the CDEC recommendation was not undertaken.

## Background

Dupilumab has a Health Canada indication for patients 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. Dupilumab is an interleukin (IL)-4 and IL-13 inhibitor. Dupilumab is available as a 200 mg or 300 mg single-use syringe with needle shield or pre-filled syringes in packs of 1 or 2. The recommended dose of dupilumab is age- and weight-specific. In adolescents aged 12 to 17 years, whose weight is less than 60 kg, two subcutaneous injections of 200 mg of dupilumab should be administered as the loading dose during the first

week, and subsequently, one 200 mg injection should be given every other week. In adolescents whose weight is greater than or equal to 60 kg, and in all adults (greater than or equal to 18 years), the recommended loading dose is 600 mg of dupilumab (two 300 mg injections), followed by 300 mg every other week.

## Submission History

Dupilumab 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. Dupilumab received a CDEC recommendation to not reimburse for this indication in July 2018.

The original CADTH systematic review of dupilumab included four double-blind RCTs, SOLO-1 (N = 671), SOLO-2 (N = 708), LIBERTY AD CAFÉ (N = 325), and LIBERTY AD CHRONOS (N = 740). All trials included patients with moderate-to-severe AD, and patients were randomized to dupilumab every week or every other week, or placebo, for a treatment duration of 16 weeks (SOLO studies and LIBERTY AD CAFÉ) or 52 weeks (LIBERTY AD CHRONOS).

Reasons for the CDEC recommendation included the lack of evidence comparing dupilumab to other drugs commonly used for managing AD, the lack of long-term safety data, concerns over generalizability of the data to those patients who would be expected to use the drug in clinical practice, and a lack of efficacy and safety data for dupilumab in patients where topical prescription therapies are not advisable.

This resubmission is based on a new indication, which expands the original indication to adolescents.

## Summary of Evidence Considered by CDEC

CDEC considered the following information prepared by CADTH: a systematic review of phase III double-blind RCTs of dupilumab and a critique of the sponsor's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with AD, and patient group–submitted information about outcomes and issues important to patients.

### Summary of Patient Input

Two patient groups, the Eczema Society of Canada and the Canadian Skin Patient Alliance provided input for this submission. Patient perspectives were obtained from online surveys, written questionnaires, interviews, and by statements provided by patients and caregivers. The following is a summary of key input from the perspective of the patient groups:

Patients described the debilitating effects of moderate-to-severe AD, including constant itching, that interferes with all aspects of life, including work, school, relationships, and sleep. Symptoms of AD negatively impact overall quality of life. During severe flares, patients may also end up bedridden, with skin covered in open wounds that may also bleed through their clothing.

Patients and caregivers describe current therapies as having limited effectiveness. For patients who do not respond adequately to topical therapies and other interventions such as judicious bathing and trigger avoidance, systemic therapies are the next step. Systemic therapies include phototherapy, which appears to not be helpful for most, according to a recent survey, and both the cost and limited number of locations are barriers to access. Oral corticosteroids may work well for some; however, patients describe terrible rebound flares when coming off the steroid. Off-label immunosuppressants are sometimes used, however these must be used temporarily due to severe side effects.

Those who tried dupilumab report significant improvements in symptoms and quality of life, including improved sleep, productivity and ability to return to work, better concentration, resumed intimate and social relationships, and increased ability to exercise. Caregivers of adolescents reported a significant improvement in mood after their children took dupilumab.

## Clinical Trials

The systematic review included six double-blind RCTs, four from the original review of dupilumab (SOLO-1 and SOLO-2, LIBERTY AD CHRONOS, and LIBERTY AD CAFÉ) as well as two new studies: one in adolescents (Study 1526) and one in adults (SOLO CONTINUE) who had moderate-to-severe AD. Study 1526 randomized 251 adolescents in a 1:1:1 manner to either dupilumab administered every two weeks or every four weeks, or placebo, over a treatment period of 16 weeks. The biweekly regimen was the focus of this review, as this is the Health Canada approved regimen. Dosing was determined by weight, 200 mg of dupilumab for those less than 60 kg and 300 mg for those weighing 60 kg or more. SOLO CONTINUE randomized responders previously enrolled in SOLO-1 and SOLO-2, to receive either dupilumab weekly or every two weeks, or dupilumab every four weeks, or every eight weeks, or placebo, over a 36-week treatment period. The SOLO-1 (N = 671) and SOLO-2 (N = 708) trials randomized patients with moderate-to-severe AD to either dupilumab every week or every other week, or placebo, over 16 weeks. LIBERTY AD CAFÉ (N = 325) was a 16-week study with the same treatment groups as SOLO-1 and -2, however all patients were on a background of topical corticosteroids; and LIBERTY AD CHRONOS (N = 740) was a 52-week study with those same treatment groups as well, and all patients were on a background of topical corticosteroids.

In Study 1526, 7% of dupilumab-treated versus 11% of placebo-treated patients discontinued treatment, while across the other studies in adults between 0% and 9% discontinued in the dupilumab groups and 5% to 20% with placebo. Limitations of the included trials included the lack of an active comparator, as all trials were placebo-controlled, of relatively short duration, and excluded patients who used topical calcineurin inhibitors or topical corticosteroids within one to two weeks before the baseline or screening visit.

## Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, CDEC discussed the following: patients with EASI-75 responses, Investigators Global Assessment (IGA) responders (score of 0 or 1 by end of treatment period), pruritus, and health-related quality of life scores. The primary outcome in four trials was IGA responder.

IGA is a 5-point scale that provides a global clinical assessment of AD severity ranging from 0 to 4, where 0 indicates clear, and 4 indicates severe AD. A decrease in score relates to an improvement in signs and symptoms. No information was found on what would constitute a minimum importance difference (MID) in patients with AD.

EASI is a scale used in clinical trials to assess the severity and extent of AD. In EASI, four disease characteristics of AD (erythema, infiltration/papulation, excoriations, and lichenification) are assessed for severity by the investigator on a scale of 0 (absent) to 3 (severe) and the scores are added up for each of the four body regions (head, arms, trunk, and legs). The assigned percentages of body surface area (BSA) for each section of the body are 10% for head, 20% for arms, 30% for trunk, and 40% for legs respectively. Each subtotal score is multiplied by the BSA represented by that region. In addition, the affected area of AD assessed as a percentage by each body region is converted to a score of 0 to 6, where the area is expressed as 0 (none), 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%). Each of the body area scores are multiplied by the area affected. Therefore, the total EASI score ranges from 0 to 72 points, with the highest score indicating worse severity of AD. The overall MID is 6.6, based on results from one study.

Scoring AD (SCORAD) assesses three components of AD: the affected BSA, severity of clinical signs, and symptoms. The severity of six specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, dryness) is assessed using a 4-point scale (i.e., none = 0, mild = 1, moderate = 2 and or severe = 3) with a maximum of 18 total points. The symptoms (itch and sleeplessness) are recorded by the patient or relative on a visual analogue scale, where 0 is no symptom and 10 is the worst imaginable symptom with a maximum possible score of 20. The SCORAD is calculated based on the three components of the AD discussed above. The maximum possible total score of SCORAD is 103; a higher score indicates poorer or a more severe condition. A difference of 8.7 points in SCORAD was estimated as the MID for the patients with AD.

The Pruritus Numeric Rating Scale (NRS) is a tool that patients used to report the intensity of their itch during a daily recall period. Patients were asked to rate their overall (average) and maximum intensity of itch experienced during the past 24 hours, based on a scale of 0 (no itch) to 10 (worst itch imaginable). The proportion of patients with improvement (reduction of greater than or equal to 3 points or greater than or equal to 4 points) of the weekly average of peak daily Pruritus NRS from baseline to week 16 was reported in the pivotal studies. The most appropriate definition of a responder on the Pruritus NRS is in the range of 3 to 4 points.

The dermatology life quality index (DLQI) is a dermatology-specific quality of life instrument. It is a 10-item questionnaire that assesses six different aspects that may affect quality of life: symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment. Each of the 10 questions is scored from 0 (not at all) to 3 (very much), resulting in an overall numeric score between 0 and 30. The higher the score, the more quality of life is impaired. Estimates of the MID have ranged from 2.2 to 6.9. The children's DLQI (CDLQI) is a variation of the DLQI, used to assess health-related quality of life in children. CDLQI can be completed by the child alone and/or with help from the parents or guardian and covers six areas of daily activities including symptoms and feelings, leisure, school or holidays, personal relationships, sleep, and treatment. No MID was identified in the literature.

The Hospital Anxiety and Depression Scale (HADS) is a patient-reported questionnaire designed to identify anxiety disorders and depression in patients at non-psychiatric medical institutions. HADS has 14 items that assess symptoms experienced in the previous week; seven items are related to anxiety and seven to depression. Patients provide responses to each item based on a 4-point Likert scale, from 0 (the best) to 3 (the worst); thus, a person can score between 0 and 21 for each subscale (anxiety and depression). Scores of 11 or more on either subscale were considered to be a definite case of psychological morbidity, while scores of 8 to 10 represented a probable case of psychological morbidity, and 0 to 7 represented a response that was not a case of psychological morbidity. No information on MID was found in the literature.

The Patient Oriented Eczema Measure (POEM) is a seven-item, questionnaire used in clinical trials to assess disease symptoms in children and adults. Based on frequency of occurrence during the past week, the seven items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) are assessed using a five-point scale: 0 indicates no days, 1 for one to two days, 2 for three to four days, 3 for five to six days, and 4 indicates every day. The maximum total score is 28; a high score is indicative of poor quality of life (0 to 2 for clear or almost clear; 3 to 7 for mild eczema; 8 to 16 for moderate eczema; 17 to 24 for severe eczema; and 25 to 28 for very severe eczema). The minimally important change of POEM in children with moderate-to-severe atopic eczema, based on one study, was as follows: a score of 3.0 to 3.9 indicates a likely clinically important change; greater than or equal to 4, indicates a very likely clinically important change.

## Efficacy

In Study 1526 with dupilumab, 24% of patients (adolescents) achieved an IGA of 0 (clear) or 1 at week 16 versus 2% in placebo at 16 weeks. The difference between dupilumab and placebo (22% [95% CI,12% to 32%], P < 0.0001) was statistically significant. Findings from the studies in adults were consistent with that of Study 1526 for this outcome; the proportion of patients with an IGA score of 0 or 1 and a reduction from baseline of two or more points at week 16 was greater in the dupilumab group compared with the placebo group, with a range in difference of proportion across trials of 26.3% (95% CI, 14.95% to 37.65%) to 27.7% (95% CI, 20.18% to 35.17%). In SOLO CONTINUE, more dupilumab than placebo patients maintained an IGA within one point of baseline by week 36.

EASI-75 responses occurred in 42% of dupilumab and 8% of placebo patients in Study 1526, and the difference between dupilumab and placebo groups (33% [95% CI, 21% to 45%], P < 0.0001) was statistically significant at week 16. In the adult studies, the proportion of patients with EASI-75 was greater in the dupilumab group compared with the placebo group across all trials, with a range in difference of proportion across trials from 32.3% (95% CI, 24.75% to 39.94%) to 45.7% (95% CI, 35.72% to 55.66%). Each trial yielded statistically significant (P < 0.0001) findings. In SOLO CONTINUE, more dupilumab than placebo patients had an EASI-75 response that they maintained at week 36.

There was an improvement (reduction) in mean SCORAD from baseline to week 16 in Study 1526 for dupilumab compared to placebo (least squares mean difference between dupilumab and placebo of –34.0 [95% CI, –43.4 to –24.6], P < 0.0001) and this difference was statistically significant and clinically significant, given the MID of 8.7 points. Across the adult trials, the least squares mean difference in SCORAD between the dupilumab and placebo groups ranged from −27.7 (95% CI, −33.46 to −21.90) to −32.9 (95% CI, −39.70 to −26.06), and these differences were statistically significant (P < 0.0001) across all trials at week 16. The LIBERTY AD CHRONOS trial included an additional assessment at week 52; all efficacy results remained consistent and statistically significant (P < 0.0001).

Mean percent change in daily peak Pruritus NRS was reduced from baseline to week 16 in the dupilumab group compared to placebo (least square mean difference of –29.0% [95% CI, –39.5 to –18.4], P < 0.0001) in Study 1526. Dupilumab also statistically significantly improved the percentage of patients achieving a reduction of at least 3 points or 4 points from baseline in weekly average of daily peak pruritus. There was an improvement in POEM scores from baseline to week 16 with dupilumab versus placebo

(least square mean difference between dupilumab and placebo of –6.3 [95% CI, –8.6 to –4.0], P < 0.0001) and these differences were statistically significant and likely clinical significant, given the MID of 4.

The proportion of patients with an improvement in their weekly average peak daily Pruritus NRS score of four or more points from baseline to week 16 was statistically greater (P < 0.0001) for patients in the dupilumab group compared with placebo across the adult trials, with a range in difference between groups of 26.5% (95% CI, 19.13% to 33.87%) to 39.1% (95% CI, 28.53% to 49.65%). Similar findings were seen for the proportion of patients with an improvement in their weekly average peak daily Pruritus NRS score of three or more points from baseline to week 16. The LIBERTY AD CHRONOS trial included an additional assessment at week 52 for the Pruritus NRS end points, which showed findings that were statistically significant (P < 0.0001) and consistent with week 16 findings. The least squares mean change in POEM score from baseline to week 16 was greater in the dupilumab group compared with the placebo group, ranging from −6.5 (95% CI, −8.02 to −5.01) to −7.6 (95% CI, −9.29 to −5.97). These findings were statistically significant (P < 0.0001) and clinically significant across adult trials. Results were similarly in favour of dupilumab versus placebo using the Pruritus NRS and the POEM score in the SOLO CONTINUE trial.

There was a larger improvement in mean CDLQI scores from baseline to week 16 with dupilumab compared to placebo (least squares mean difference between dupilumab and placebo of –3.4 [95% CI, –5.0 to –1.8], P < 0.0001) at week 16 in Study 1526. The mean improvement in HADS total scores from baseline to week 16 was not statistically significant for dupilumab versus placebo (least squares mean difference between groups of –1.3 [95% CI, –3.30 to 0.76] P = 0. 0.1691). In adults, the least squares mean change in DLQI score from baseline to week 16 was greater in the dupilumab group compared with the placebo group, ranging from −4.0 (95% CI, −5.16 to −2.80) to −5.7 (95% CI, −6.86 to −4.47). These findings were both statistically significant (P < 0.0001) and potentially clinically relevant based on an MID range of 2.2 to 6.9. The 52-week data from the LIBERTY AD CHRONOS trial and 36-week data from SOLO CONTINUE trial for the DLQI were statistically significant (P < 0.0001) in favour of dupilumab and consistent with week 16 findings.

Across the SOLO 1, SOLO 2, and LIBERTY AD CHRONOS trials, the difference in least squares mean change from baseline in EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) index utility score between the dupilumab and placebo groups ranged from 0.060 (95% CI, 0.02 to 0.10) to 0.167 (95% CI, 0.12 to 0.21).

## Harms (Safety)

Overall adverse events occurred in 65% to 74% of patients in the dupilumab group and in 65% to 82% of those in the placebo group across the included studies. The most common adverse events, in both groups, were upper respiratory tract infections and AD.

Serious adverse events occurred in 0% to 5% of patients in the dupilumab group and 1% to 9% of those in the placebo group across studies.

Withdrawals due to adverse events occurred in 0% to 2% of patients in the dupilumab group and 1% to 5% in the placebo group across studies.

Notable harms for this review included conjunctivitis and injection site reactions, and there were no clear and consistent differences between dupilumab and placebo groups for these outcomes.

Longer-term safety extensions with follow-up extending to 36 weeks did not reveal any new safety issues.

## Indirect Evidence

Three potentially relevant indirect treatment comparisons were identified in the literature comparing dupilumab to other treatments of patients with moderate-to-severe AD. These indirect treatment comparisons were not summarized due to their significant methodological limitations.

## Cost and Cost-Effectiveness

At the sponsor–submitted price of $959.94 per injection regardless of strength, the first-year cost of dupilumab is $25,918 per patient and the annual maintenance cost is $24,958 per patient.

The sponsor submitted a cost-utility analysis comparing dupilumab plus SOC with SOC (i.e., topical therapy) alone in patients 12 years or older with moderate-to-severe AD for whom topical prescription therapies failed to achieve effective disease control or were not advisable, in line with the Health Canada indication. The model structure included a decision tree that captured a short-term (one year) phase of treatment response assessments and a Markov state-transition model for the maintenance phase over a lifetime horizon (86 years). In the short-term phase, treatment response was modelled as a greater than or equal to 50% improvement in baseline EASI score at weeks 8 and 52, from the Study 1526 and LIBERTY AD CHRONOS trials respectively. Patients who met this criterion at both assessment points entered the response state by treatment in the Markov state-transition model (long-term model). Patients who did not respond to dupilumab plus SOC moved to SOC alone. The Markov model incorporated a one-year cycle time and consisted of four health states: dupilumab plus SOC treatment with response, SOC treatment with response, SOC treatment without response, and death. Age- and sex-specific death rates were sourced from the National Life Tables for Canada. The sponsor also provided a scenario analysis for the reimbursement request population — patients who were also refractory to or ineligible for, systemic immunosuppressant therapies.

CADTH identified the following key limitations with the sponsor's submitted economic analysis:

- Relevant comparators, such as immunosuppressants (e.g., methotrexate, cyclosporine) prescribed to treat moderate-to-severe AD, were not included as comparators.
- 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 sponsor incorporated treatment-specific utility values, which does not reflect best practice. Further, the methodology used to derive these values was associated with substantial uncertainty.
- The utility estimates lacked face validity in several respects (e.g., the utility weight for dupilumab plus 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.
- The durability of treatment response beyond the trial duration remains uncertain.

CADTH undertook a reanalysis that excluded caregiver utilities; included alternate measures for treatment response and non-response, utility, and durability of response; as well as, considered macro-level costing. The ICER for dupilumab plus SOC compared with SOC alone was $136,025 per additional QALY gained. CADTH undertook a scenario analysis for the reimbursement request population (patients who are also refractory to or ineligible for systemic immunosuppressant therapies), which resulted in a similar ICER ($133,877 per QALY gained). CADTH also performed an analysis on the base case which incorporated EASI-75 as the response definition and reduced the ICER to $120,738 per QALY. Price reduction analyses were not undertaken on the patient population recommended by CDEC.

These results, which were driven by the durability of effect between weeks 16 and 52, are highly uncertain. CADTH could neither assess the cost-effectiveness of dupilumab plus 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 dupilumab's cost-effectiveness differed in patients with moderate versus severe AD. As a result, the results of the economic analysis are uncertain.

## CDEC Members

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

## March 18, 2020 Meeting

## Regrets

One CDEC member did not attend

## Conflicts of Interest

None