CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

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

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that dupilumab not be reimbursed for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

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Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that dupilumab not be reimbursed for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Reasons for the Recommendation:

1. No evidence was available that compared dupilumab with other drugs commonly used in the treatment of AD. The four phase III, placebo-controlled, randomized controlled trials (RCTs) (three 16-week trials [SOLO 1, SOLO 2, and LIBERTY AD CAFÉ] and one 52-week trial [LIBERTY AD CHRONOS]) reviewed were not designed to compare dupilumab with other drugs commonly used in the treatment of atopic dermatitis. Although these trials demonstrated that a statistically significantly greater percentage of patients had improvements in AD severity, symptoms, and quality of life with dupilumab treatment compared with placebo, the magnitude of clinical benefit with dupilumab compared with existing alternative treatments is unknown.
2. There are several notable gaps in the clinical evidence regarding dupilumab, including data to assess the long-term safety of dupilumab, concerns with the generalizability of the trial results to patients who would be expected to use dupilumab in clinical practice, and an absence of efficacy and safety data for the use of dupilumab in patients where topical prescription therapies are not advisable.

Discussion Points:

- CDEC noted that for patients with AD who do not achieve disease control with appropriate skin care measures, topical corticosteroids (TCS) and/or topical calcineurin inhibitors (TCIs) or phototherapy, the standard of care typically consists of treatment with intermittent courses of immunosuppressive drugs. The Committee recognized that dupilumab is the first Health Canada–approved drug for use in patients with moderate-to-severe AD who are not adequately controlled with topical therapies, and noted that dupilumab would likely be used as an alternative treatment option for patients who are inadequately controlled with immunosuppressive drugs or have contraindications to such drugs. However, the Committee concluded that the potential advantages of using a Health Canada–approved drug in this population did not offset the disadvantages associated with using a drug that lacks comparative efficacy and safety data.
- 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' (three trials) and 52 weeks' (one trial) duration; therefore, there are no safety data for dupilumab beyond one year of treatment. Longer-term safety data were needed for the Committee to appropriately assess the benefit versus risk profile of dupilumab.
- CDEC noted that patients who were using TCS, a standard treatment of AD, or TCIs within one week of the baseline visit were excluded from SOLO 1, SOLO 2, and LIBERTY AD CHRONOS, while the LIBERTY AD CAFÉ trial excluded patients who used TCIs within one week of the screening visit. The LIBERTY AD CHRONOS trial also excluded patients who experienced important side effects to topical medications (e.g., intolerance, hypersensitivity). These exclusion criteria limit the generalizability of the efficacy and safety results reported in the trials to patients who would be expected to use dupilumab in clinical practice and would frequently use TCS or a TCI regularly to treat their AD.
- CDEC noted that only 2.2% and 1.7% of patients randomized in the SOLO 1 and SOLO 2 trials, respectively, were considered to be intolerant to TCS. Therefore, there is a paucity of efficacy and safety data for the use of dupilumab in the subset of patients for whom topical prescription therapies are not advisable.
- CDEC noted that the patient-group input for this review indicated that patients with AD often experience difficulty with their topical treatment plans, including challenges with adherence to topical therapies. The clinical expert consulted by the CADTH Common Drug Review (CDR) noted that the use of topical treatments between flares is intended to keep a patient's AD under control, and efforts to overcome the challenges associated with adherence to topical therapies has the potential to reduce the need for systemic medications such as dupilumab for some patients.

Background:

Dupilumab has a Health Canada–approved indication 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 can be used with or without TCS. Dupilumab is a recombinant human IgG4 monoclonal antibody. It is available as a subcutaneous injection, and the Health Canada–approved dose is 150 mg/mL.

Summary of CDEC Considerations:

The Committee considered the following information prepared by CDR: a systematic review of RCTs of dupilumab and a critique of the manufacturer's pharmacoeconomic evaluation. The Committee also considered input from a clinical expert with experience treating patients with AD and patient group–submitted information about outcomes and issues important to patients with AD.

Patient Input Information:

The Eczema Society of Canada (ESC) provided input for the CDR submission for dupilumab. Patient perspectives were obtained by ESC from an online survey and one-on-one interviews. The following is a summary of key input from the perspective of the patient group:

- AD has a significant impact on patients' daily lives. Patients describe an intense itch that can persist all day and often worsens at night, thereby affecting sleep. Living with chronic itch, pain, and chronic cycles of flares (acute worsening of the disease) takes a significant toll on quality of life. Approximately 87% of patients reported that their day-to-day quality of life is negatively impacted by interrupted and/or loss of sleep, anxiety, depression, social isolation, poor self-esteem, and suicidal thoughts.
- Caregivers are also impacted and reported feelings of helplessness and frustration, while the patient is suffering with a condition that cannot be controlled and continues to flare. The caregivers indicated they also experienced sleep loss, along with anxiety and depression.
- Respondents noted the following issues with their current AD treatment: difficulty dressing after applying treatments (52% of respondents); feeling uncomfortable (49%); difficulty finding time during the day to apply the medications (44%); difficulty adhering to a topical treatment plan (38%); topical medications causing interference with work and/or day-to-day life (38%); and physical pain when applying treatments (32%). Approximately 63% of respondents who have tried off-label systemic therapies reported the therapies did not work well in managing their AD.
- Patients are seeking a treatment that will break the cycle of flares and manage the itch. Patients also expect the new medication to improve their quality of life.

Clinical Trials

The CDR systematic review included four phase III, double-blind, parallel-group, placebo-controlled RCTs of patients with moderate-to-severe AD. SOLO 1 (N = 671) and SOLO 2 (N = 708) randomized patients with AD in a 1:1:1 treatment ratio of: dupilumab 600 mg on day 1 followed by 300 mg weekly; dupilumab 600 mg on day 1 followed by 300 mg every other week; or weekly subcutaneous injections of placebo, respectively, for 16 weeks. LIBERTY AD CHRONOS (N = 740) randomized patients with AD in a 3:1:3 ratio for treatment with the following: 300 mg of dupilumab weekly following a loading dose of 600 mg on day 1; 300 mg of dupilumab every other week following a loading dose of 600 mg on day 1; or weekly subcutaneous injections of placebo, respectively, for 52 weeks. LIBERTY AD CAFÉ randomized patients with AD who had either a history of prior cyclosporine-A (CSA) exposure and either inadequate response to CSA or intolerance and/or unacceptable toxicity, or a history of being CSA-naive and not eligible for CSA due to medical contraindications or other reasons, in a 1:1:1 ratio for treatment with the following: dupilumab 600 mg on day 1 followed by 300 mg weekly; dupilumab 600 mg on day 1 followed by 300 mg every other week; or weekly subcutaneous injections of placebo, respectively, for 16 weeks. Patients in LIBERTY AD CHRONOS and LIBERTY AD CAFÉ were concomitantly treated with medium-potency TCS daily on areas of the skin with active lesions. No active comparator trials met the CDR review criteria.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following:

- Severity of AD was assessed using the Investigator Global Assessment (IGA) score, the Eczema Area and Severity Index (EASI), and the Scoring Atopic Dermatitis (SCORAD) tool.
    - The IGA is a five-point scale ranging from 0 to 4 that provides a global clinical assessment of AD severity (where 0 indicates clear, 2 is mild, 3 is moderate, and 4 indicates severe AD). No minimal clinically important difference (MCID) was identified for patients with AD.
    - The EASI assesses four disease characteristics of AD (erythema, infiltration/papulation, excoriations, and lichenification). These were assessed for severity by the investigator on a scale of 0 (absent) to 3 (severe) for each of four body regions (head, arms, trunk, and legs), and weighted by body surface area for each region. A total EASI score can range from 0 to 72 points, with higher scores indicating greater severity. An MCID of 6.6 points has been reported for patients with AD.
    - The SCORAD assesses three components of AD: the affected body surface area, the severity of clinical signs, and the symptoms and results, providing a maximum score of 103, with a higher score indicating a more severe condition. An MCID of 8.7 points has been reported for patients with AD.
- Symptom reduction was assessed using the Pruritus Numerical Rating Scale (NRS) and the Patient-Oriented Eczema Measure (POEM).
    - The Pruritus NRS was used for patients to report, in a daily diary, the overall and maximum intensity of their itch on a scale of 0 to 10. No MCID was identified for patients with AD.
    - The seven-item POEM was used to assess the frequency of occurrence during the past week of the following using a five-point scale: dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping. Higher scores on a scale from 0 to 28 indicate poor quality of life and increasing severity of eczema. The MCID for the POEM was determined to be 3.4 points in patients with AD.
- Health-related quality of life was assessed using the Dermatology Life Quality Index (DLQI) and the EuroQol 5-Dimensions (EQ-5D) 3-Levels questionnaire (EQ-5D-3L).
    - The DLQI assessed the impact of a (general) dermatological disease on a patient's quality of life over a one-week period by assessing the following six dimensions: symptoms and feelings, daily activities, leisure, work/school, personal relationships, and treatment. Scores range from 0 to 30, with higher scores indicating poorer quality of life. No MCID was identified for patients with AD.
    - The EQ-5D is a generic quality-of-life instrument that includes the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-3L was used to assess these dimensions across three levels of severity (no problem, some problems, severe problems). No MCID was identified for patients with AD.
- Adverse events (AEs), serious adverse events (SAEs), withdrawal due to adverse events (WDAEs), notable harms (AD flares, conjunctivitis), and use of rescue medication.

Across all studies, the proportion of patients with EASI-75 (a 75% or greater improvement from baseline) at week 16 was the primary efficacy end point. The proportion of patients with an IGA score of 0 or 1 (on a five-point scale) and a reduction from baseline of two or more points at week 16 was an additional primary end point for the SOLO trials and LIBERTY AD CHRONOS, and a secondary end point for LIBERTY AD CAFÉ.

Efficacy

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% confidence interval [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. 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%). Each trial yielded statistically significant findings ($P < 0.0001$). While no relevant MCID was found in the literature for the IGA for patients with AD, the clinical expert consulted for this review indicated that the findings were relevant clinically. The least

squares mean percentage change in SCORAD from baseline was greater in the dupilumab group compared with the placebo group. Across trials, the least squares mean difference in SCORAD score 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 ($P < 0.0001$).

The proportion of patients with an improvement (reduction in score) 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 all 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 (MCID = 3.48) across all trials.

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 MCID range of 2.2 to 6.9. The LIBERTY AD CHRONOS trial included an additional assessment at week 52 for the DLQI end point, which showed findings that were statistically significant ($P < 0.0001$) 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 EQ-5D-3L 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 and Tolerability)

- Overall AEs were similar compared with placebo. The most common class of AEs was infections and infestations. Consistently across trials, conjunctivitis (and general eye disorders) affected more patients in the dupilumab group compared with the placebo group.
- In the SOLO 1, SOLO 2, LIBERTY AD CHRONOS, and LIBERTY AD CAFÉ trials, there were fewer SAEs with dupilumab compared with placebo; across trials at week 16, SAEs were reported in 1.7% to 4.7% of patients in the dupilumab group and 3.5% to 9.3% in the placebo group. The most common SAEs related to [redacted]
- Rescue medication was used in more patients in the placebo group compared with dupilumab. Rescue medication was used in 21.0% and 16.1% of patients in the dupilumab group, and in 51.8% and 52.1% of patients in the placebo group in the SOLO trials. In LIBERTY AD CHRONOS and LIBERTY AD CAFÉ, rescue medication was used in 10.9% and 3.7% of patients in the dupilumab group, and 34.6% and 14.8% of patients in the placebo group. Across all trials, the most common form of rescue medication was potent (group III) TCS.

Cost and Cost-Effectiveness

Dupilumab is available as a 150 mg/mL solution in a pre-filled syringe at a manufacturer-submitted price of $1,153.85 per 300 mg dose. The first-year cost of dupilumab is $31,154 and $30,000 annually thereafter.

The manufacturer submitted a cost-utility analysis of dupilumab as an add-on to current standard of care (SOC) in patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies. The comparator was current SOC, which was defined as mid-potency TCS or TCIs. 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 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.

The analyses were conducted from the perspective of the publicly funded health care system in Canada over a lifetime time horizon, with costs and benefits discounted at an annual rate of 1.5%. The manufacturer reported that dupilumab plus SOC was associated with an incremental cost-utility ratio (ICUR) of $89,723 per quality-adjusted life-year (QALY) compared with SOC alone.

CDR identified the following key limitations with the manufacturer's economic submissions:

- The manufacturer's analysis excluded relevant comparators (such as alitretinoin, immunosuppressants, and phototherapy).
- The effects of compliance were not fully incorporated within the economic model. The manufacturer assumed that poor compliance with dupilumab would reduce drug treatment costs without any effect on quality of life or treatment response. Adjusting compliance rates to reflect the values reported in the LIBERTY AD CHRONOS trial resulted in a higher ICUR, given the increased costs associated with dupilumab.
- Treatment-specific utility values were applied based on a regression analysis, with responders on dupilumab plus SOC assumed to maintain quality of life throughout their lifetime, while treatment waning for SOC was assumed after the first year. The model was sensitive to changing the treatment-utility values and to varying the assumptions around treatment waning.
- An annual discontinuation rate of 2.4% for dupilumab was applied, which was lower than reported for other biologics and lower than observed in the SOLO trial. Applying a discontinuation rate of 6.3% based on the SOLO trial did not significantly impact the results.
- The cost-effectiveness of dupilumab plus SOC in patients where topical prescription therapies are not advisable is unknown.

CDR undertook a reanalysis, revising the discontinuation rate, the compliance rate, and the approach to modelling health state utility values. Based on the CDR reanalysis, the ICUR for dupilumab plus SOC compared with SOC alone in patients not adequately controlled by topical prescription therapies was $579,672 per QALY gained. Based on the CDR reanalysis, a price reduction of 84% is required to achieve an ICUR of $50,000 per QALY.

CDEC Members:

April 11, 2018 Meeting

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets:

None

Conflicts of Interest:

None

June 20, 2018 Meeting

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets:

None

Conflicts of Interest:

None