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CADTH Reimbursement Recommendation

Dupilumab (Dupixent)

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

Sponsor: Sanofi-Aventis Canada Inc.

Final recommendation: Reimburse with conditions

This recommendation supersedes the CADTH Canadian Drug Expert Committee recommendation for this drug and indication dated April 24, 2020.

CADTH

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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.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Dupixent?

CADTH recommends that Dupixent be reimbursed by public drug plans for the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable, if certain conditions are met.

This recommendation supersedes the CADTH Canadian Drug Expert Committee recommendation for this drug and indication on April 24, 2020. A Request for Advice was filed in 2022 by public drug programs to address an inquiry regarding the 2020 reimbursement conditions.

Which Patients Are Eligible for Coverage?

Dupixent should only be covered for patients who previously tried and did not experience improvement with or are unable to use other treatments. These treatments include the highest dose of topically applied drugs combined with phototherapy (where available), and the highest dose of topically applied drugs and at least 1 of the following: methotrexate, cyclosporine, mycophenolate mofetil, or azathioprine.

What Are the Conditions for Reimbursement?

Dupixent should only be reimbursed if prescribed by a dermatologist, allergist, clinical immunologist, or pediatrician, and if the cost of Dupixent is reduced.

Why Did CADTH Make This Recommendation?

- In 5 clinical trials with adults and 1 with adolescents, Dupixent reduced AD severity and symptoms compared to placebo.
- Dupixent may meet some needs that are important to patients, including reducing AD severity and symptoms and improving health-related quality of life (HRQoL).
- Based on CADTH's assessment of the health economic evidence, Dupixent does not represent good value to the health care system at the public list price and requires at least a 54% price reduction. A price reduction analysis on the population aligned with the original 2020 CDEC recommendation was not undertaken. The 2022 Request for Advice did not include additional economic analyses.

Additional Information

What Is AD?

AD is a condition that affects the skin, causing dry, red skin that is extremely itchy. Constant scratching can cause the skin to split and bleed, which can cause infections. Oozing and weeping sores can occur in more severe forms. Severe AD can be physically incapacitating and cause anxiety or depression. Lifetime prevalence is estimated at up to 17% in Canada.

Unmet Needs in AD

There is no cure for AD; treatment aims to provide symptom relief and control in the longer term. Although many treatments for AD are approved in Canada, some patients' symptoms may not be controlled with existing drugs, so other treatment options are needed.

How Much Does Dupixent Cost?

Treatment with Dupixent is expected to cost approximately $25,918 per patient during the first year; the annual maintenance cost is $24,958 per patient.

Recommendation

This recommendation supersedes the CADTH Canadian Drug Expert Committee (CDEC) recommendation for this drug and indication dated April 24, 2020.

The CADTH Canadian Drug Expert Committee (CDEC) recommends that dupilumab be reimbursed for the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable, only if the following conditions are met.

Conditions for Reimbursement

Initiation Criteria

1. Patients must have had an adequate trial (with a documented refractory disease), or were intolerant (with documented intolerance), or are ineligible for each of the following therapies:
    1.1. maximally tolerated medical topical therapies for AD combined with phototherapy (where available), and
    1.2. maximally tolerated medical topical therapies for AD combined with at least 1 of the 4 systemic immunomodulators (methotrexate, cyclosporine, mycophenolate mofetil, or azathioprine).
2. 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.
3. The maximum duration of initial authorization is 6 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) 6 months after treatment initiation.
2. The physician must provide proof of maintenance of EASI-75 response from baseline every 6 months for subsequent authorizations.

Prescribing Conditions

1. The patient must be under the care of a dermatologist, allergist, clinical immunologist, or pediatrician who has expertise in the management of moderate-to-severe AD.
2. Dupilumab should not be used in combination with phototherapy, any immunomodulatory drugs (including biologics or a Janus kinase [JAK] inhibitor treatment) for moderate-to-severe AD.

Pricing Conditions

Reduction in price.

Reasons for the Recommendation

1. Dupilumab demonstrated superiority in improving signs and symptoms of AD, as well as HRQoL, when compared with placebo in adolescents (1 randomized controlled trial [RCT]) and adults (5 RCTs) who had moderate-to-severe AD. Patients studied were those with an inadequate response to topical therapies, or for whom topical therapies were not advisable (1 RCT based on the adolescent population and 4 RCTs based on the adult population), and for whom 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 have experienced toxicities.
3. During discussions on the request for advice, CDEC determined that the initiation and prescribing conditions for dupilumab should be updated to reflect conditions applied to recent drugs for AD in this patient population, based on the dupilumab trials, clinical expert opinion, and stakeholder input.
4. Conventional approaches to moderate-to-severe AD refractory to topical therapies have, for a number of years, included older immunomodulatory drugs. Concerns about their long-term safety continue; however, clinical experience with systemic immunomodulators is extensive and the costs are modest compared to novel drugs. In addition, the percentage of patients with prior exposure to at least 1 systemic treatment for AD in the included trials were: 26.3% in the SOLO 1 study, 31.1% in the SOLO 2 study, 33.6% in the LIBERTY AD CHRONOS study, and 20.8% in Study 1526. Because patients enrolled in the LIBERTY AD CAFÉ study could have prior cyclosporine exposure, 77.5% of enrolled participants in that study had received at least 1 prior systemic immunosuppressant. CDEC accepted the opinion of the clinical expert as well as feedback from the drug plans and clinicians indicating that at least 1 conventional immunomodulatory drug should be attempted before dupilumab is used for refractory AD.
5. In response to the request for advice, CDEC noted that the initial length of authorization for dupilumab should remain at 6 months, given its mechanism of action and timing of onset of effect. This was aligned with how patients would be treated in clinical practice in Canada.
6. Accurate diagnosis and follow-up of patients with refractory moderate-to-severe AD is important to ensure that dupilumab is prescribed to the most appropriate patients. In addition, there are several treatment options that may be considered when selecting the most appropriate therapy for patients, which is best determined by dermatologists, allergists, clinical immunologists, or pediatricians who have expertise in the management of moderate-to-severe AD, and who are familiar with this treatment paradigm.

7. There is no evidence to demonstrate a beneficial effect of dupilumab when used in combination with phototherapy, any immunomodulatory drugs (including biologics), or other JAK inhibitor treatment for moderate-to-severe AD.
8. At the sponsor-submitted price of $959.94 for each of the 200 mg and 300 mg injections of dupilumab, 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), and 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 3 or 4.
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.
4. The clinical expert noted that an "adequate trial" for patients with AD who undergo therapy with phototherapy, methotrexate, cyclosporine, mycophenolate mofetil, and azathioprine is defined as follows:
    4.1. For phototherapy: the typical duration would be considered 12 weeks (3 times per week).
    4.2. For methotrexate: an adequate trial would be 10 mg to 20 mg per week for 12 weeks.
    4.3. For cyclosporine: an adequate trial would be 2.5 mg/kg to 5 mg/kg per day for 12 weeks.
    4.4. For mycophenolate mofetil: an adequate trial would be 1 g twice daily for 12 weeks.
    4.5. For azathioprine: an adequate trial would be 1.5 to 2.5 mg/kg/day for 12 weeks.

Discussion Points

- CDEC noted that, overall, the trial results were generalizable to the population of people in Canada with moderate-to-severe AD. However, patients who were using topical calcineurin inhibitors or topical corticosteroids (which are standard treatments for AD) within 1 to 2 weeks of the baseline visit were excluded from Study 1526 and the SOLO 1, SOLO 2, and

LIBERTY AD CHRONOS trials, while the LIBERTY AD CAFÉ trial excluded patients who used topical calcineurin inhibitors within 1 week of the screening visit.

- CDEC noted that AD is a chronic, relapsing condition with which patients often experience episodes of worsening symptoms throughout their lives. The included trials were limited to durations of 16 weeks (4 trials) and 52 weeks (1 trial). The SOLO CONTINUE trial 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 1 year of treatment, and therefore, the longer-term safety of dupilumab beyond 1 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 population of people living in Canada, 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; 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.
- When discussing the request for advice, CDEC acknowledged that the conditions for reimbursement for dupilumab should be updated to reflect recommendation of newer therapies. In particular, the committee noted that some clinical experts no longer support initiation criteria requiring previous treatment with, and failure of, cyclosporine.

Background

Dupilumab has a Health Canada indication for 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. 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 (aged 18 years or older), the recommended loading dose is 600 mg of dupilumab (two 300 mg injections), followed by 300 mg every other week.

Submission History

Dupilumab has been reviewed twice by CADTH for the treatment of AD: as a new drug in 2018 and as a resubmission for an expanded indication in 2020. The initial review for dupilumab was 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. The original CADTH systematic review of dupilumab included 4 double-blind RCTs, the SOLO-1 (N = 671), SOLO-2 (N = 708), LIBERTY AD CAFÉ (N = 325), and LIBERTY AD CHRONOS (N = 740) trials. All trials included patients with moderate-to-severe atopic dermatitis, and patients were randomized to dupilumab every week or every other week, or placebo, for a treatment duration of 16 weeks (in the SOLO studies and the LIBERTY AD CAFÉ trial) or 52 weeks (in the LIBERTY AD CHRONOS trial). In July 2018, CDEC issued a recommendation that dupilumab should not be reimbursed for this indication. 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 patients who would be expected to use the drug in clinical practice, and a lack of efficacy and safety data for dupilumab in patients for whom topical prescription therapies are not advisable.

A resubmission was subsequently filed by the sponsor for a new indication, which expanded the initial patient population limited to adults to include adolescents. In April 2020, CDEC issued a recommendation that dupilumab should be reimbursed for the treatment of AD only if conditions are met.

A request for advice was filed in July 2022 by the public drug programs that participate in the CADTH reimbursement review process to address discordant reimbursement conditions between dupilumab and JAK inhibitors (upadacitinib and abrocitinib), which were recommended to be reimbursed with conditions for the treatment of AD.

Summary of Evidence Considered by CDEC: 2020 Resubmission

This section reflects the summary of evidence considered by CDEC during deliberations for the April 2020 recommendation.

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 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), which interfere 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 not to 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 severe rebound flares when coming off steroids. Off-label immunosuppressants are sometimes used, but these must be used temporarily due to severe side effects.

Those who have 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 6 double-blind RCTs, 4 from the original review of dupilumab (the SOLO-1 and SOLO-2, LIBERTY AD CHRONOS, and LIBERTY AD CAFÉ trials) as well as 2 new studies: 1 with adolescents (Study 1526) and 1 with adults (the SOLO CONTINUE study) who had moderate-to-severe AD. Study 1526 randomized 251 adolescents in a 1:1:1 manner to either dupilumab administered every 2 weeks or every 4 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 weighing less than 60 kg and 300 mg for those weighing 60 kg or more. The SOLO CONTINUE study randomized responders previously enrolled in the SOLO-1 and SOLO-2 studies, to receive either dupilumab weekly or every 2 weeks, or dupilumab every 4 weeks or every 8 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. The LIBERTY AD CAFÉ study (N = 325) was a 16-week study with the same treatment groups as the SOLO-1 and SOLO–2 studies; however, all patients were on a background regimen of topical corticosteroids. The LIBERTY AD CHRONOS study (N = 740) was a 52-week study with those same treatment groups as well, and all patients were on a background regimen 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 1 to 2 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 HRQoL scores. The primary outcome in 4 trials was IGA responders.

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 minimal 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, 4 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 4 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. 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 the worst severity of AD. The overall MID is 6.6, based on results from 1 study.

Scoring AD (SCORAD) assesses 3 components of AD: the affected BSA, severity of clinical signs, and symptoms. The severity of 6 specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, and dryness) is assessed using a 4-point scale (i.e., none = 0, mild = 1, moderate = 2, or severe = 3), with a maximum of 18 total points. The symptoms (itching and sleeplessness) are recorded by the patient or relative on a visual analogue scale, where 0 represents no symptom and 10 represents the worst imaginable symptom, with a maximum possible score of 20. SCORAD is calculated based on the 3 components of AD discussed above. The maximum possible total SCORAD score is 103; a higher score indicates a more severe condition. A difference of 8.7 points in SCORAD was estimated as the MID for 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 previous 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) in 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 6 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 HRQoL in children. CDLQI can be completed by the child alone and/or with help from the parents or guardian and covers 6 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 nonpsychiatric medical institutions. HADS has 14 items that assess symptoms experienced in the previous week; 7 items are related to anxiety and 7 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). A score of 11 or more on either subscale was considered to represent a definite case of psychological morbidity, while a score of 8 to 10 represented a probable case of psychological morbidity, and a score of 0 to 7 represented a response that was not considered a case of psychological morbidity. No information on MID was found in the literature.

The Patient Oriented Eczema Measure (POEM) is a 7-item questionnaire used in clinical trials to assess disease symptoms in children and adults. Based on frequency of occurrence during the previous week, the 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) are assessed using a 5-point scale: 0 indicates no days, 1 indicates 1 to 2 days, 2 indicates 3 to 4 days, 3 indicates 5 to 6 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 1 study, was as follows: a score of 3.0 to 3.9 indicated a likely clinically important change, while a score greater than or equal to 4 indicated a very likely clinically important change.

Efficacy

In Study 1526, 24% of patients (adolescents) taking dupilumab achieved an IGA of 0 (clear) or 1 at week 16, versus 2% in the placebo group 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 with adults were consistent with Study 1526 for this outcome; the proportion of patients with an IGA score of 0 or 1 and a reduction from baseline of 2 or more points at week 16 was greater in the dupilumab groups compared with the placebo groups, 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 the SOLO CONTINUE study, more patients in the dupilumab group than in the placebo group maintained an IGA within 1 point of baseline by week 36.

EASI-75 responses occurred in 42% of patients in the dupilumab group and 8% of patients in the placebo group in Study 1526, and the difference between the 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 groups compared with the placebo groups 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 the SOLO CONTINUE study, more patients in the dupilumab group than in the placebo group had an EASI-75 response that was maintained at week 36.

There was an improvement (reduction) in mean SCORAD score 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 for 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 the placebo group (least squares 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 squares 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 clinically significant, given the MID of 4.

The proportion of patients with an improvement in their weekly average peak daily Pruritus NRS score of 4 or more points from baseline to week 16 was statistically greater (P < 0.0001) for patients in the dupilumab groups compared with the placebo groups 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 observed for the proportion of patients with an improvement in their weekly average peak daily Pruritus NRS score of 3 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 POEM score in the SOLO CONTINUE trial.

There was a greater 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 groups compared with the placebo groups, 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 the MID range of 2.2 to 6.9. The 52-week data from the LIBERTY AD CHRONOS trial and 36-week data from the SOLO CONTINUE trial for the DLQI were statistically significant (P < 0.0001) in favour of dupilumab, and were 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 groups and in 65% to 82% of those in the placebo groups across the included studies. The most common adverse events, in both the dupilumab and placebo groups, were upper respiratory tract infections and AD.

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

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

Notable harms for this review included conjunctivitis and injection site reactions, and there were no clear and consistent differences between the 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 for 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 aged 12 years or older with moderate-to-severe AD for whom topical prescription therapies failed to achieve effective disease control or were not advisable, in line with the Health Canada indication. The model structure included a decision tree that captured a short-term (1-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 1-year cycle time and consisted of 4 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 nonresponse, utility, and durability of response; and 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 that 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 not 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; it also was not 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.

Summary of Evidence Considered by CDEC: 2022 Request for Advice

Context for the Request for Advice

In 2020, CDEC recommended that dupilumab be reimbursed for the treatment of AD only if the conditions for reimbursement were met. Subsequently, 3 new drugs for adult patients

with moderate-to-severe AD were reviewed in 2022. CDEC recommended that 2 out of the 3 be reimbursed with clinical criteria and/or conditions (upadacitinib [Rinvoq] and abrocitinib [Cibinqo]), while CDEC recommended not to reimburse the third (tralokinumab [Adtralza]). While the conditions for reimbursement for upadacitinib and abrocitinib are very similar, they differ from those issued for dupilumab.

The public drug programs that participate in the CADTH reimbursement review process have indicated that the harmonization of reimbursement conditions would help avoid implementation issues that may arise from the CADTH recommendations for dupilumab, upadacitinib, and abrocitinib. Feedback has been received from clinical specialists involved in the diagnosis and management of AD that the criteria included in the dupilumab recommendations are not reflective of current clinical practice. Given the discrepancy between the final recommendations and feedback received from some clinicians, the drug programs that participate in the CADTH reimbursement review process are requesting that CDEC provide advice regarding the following question:

- Should the reimbursement conditions recommended for dupilumab be updated to align with those recommended for upadacitinib (and abrocitinib)?

In 2021, dupilumab received a Notice of Compliance from Health Canada for an expansion in indication from 12 years of age to 6 years of age and older. Thus, it is currently approved for the treatment of patients aged 6 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. However, this current request for advice is based on the indication reviewed by CDEC in 2020, for patients aged 12 years and older. The expanded indication with the younger age group has not been reviewed by CADTH at the time the request for advice was filed; thus, it is out of scope for this review.

Sources of Information Used by the Committee

For the request for advice, the committee considered the following information:

- input from 1 clinical expert with experience in treating patients with AD
- input from 3 patient groups: The Eczema Society of Canada; and joint input from The Canadian Skin Patient Alliance and Eczéma Québec (EQ)
- input from 3 clinician groups: the Canadian Dermatology Association, the Dermatologist and Allergist Group Managing Atopic Dermatitis, and Origins Dermatology Centre
- input from Sanofi-Aventis Canada Inc.
- the 2020 recommendation for dupilumab (Dupixent) for the treatment of AD.

The scope of a request for advice is limited to the question(s) posed by the public drug programs or the pan-Canadian Pharmaceutical Alliance (pCPA); therefore, only pertinent information necessary to respond to the request was reviewed. No additional clinical or economic information was included in this request for advice.

Stakeholder Perspectives

Overall, the clinical expert and stakeholders consulted by CADTH (clinician groups, patient groups, and manufacturer of dupilumab) indicated that alignment of the reimbursement conditions for dupilumab, upadacitinib, and abrocitinib would be reasonable, in particular those that guide who will receive these drugs (initiation) and who would be able to prescribe these agents.

Patient Group Input

Patient groups agreed that some reimbursement conditions recommended for dupilumab should be updated to align with those recommended for upadacitinib to reduce inequities and barriers to accessing drugs for AD. There was general agreement to update the initiation and prescribing criteria. However, the Canadian Skin Patient Alliance and EQ recommended keeping the duration of initial authorization at 6 months, as this duration reflected the unique considerations for dupilumab. They also proposed involvement of special sites to be included as part of the initiation criteria as an alternative to meeting the criteria for overall severity.

Clinical Expert Input

The clinical expert consulted by CADTH felt that alignment of the reimbursement conditions for dupilumab, upadacitinib, and abrocitinib is reasonable. Generally, all 3 drugs are expected to be used as second-line systemic therapy after failure of or intolerance to systemic immunosuppressives in the treatment of AD. The specified prescribing specialists (general dermatologists, pediatric dermatologists, allergists/immunologists, or pediatricians with an interest in AD) should align for all 3 drugs. However, it would be reasonable to continue with the original renewal criteria (duration of initial reimbursement), which differs between dupilumab and the 2 JAK inhibitors based on the different mechanism of action.

Clinician Group Input

All clinician groups agreed with making some updates with respect to current reimbursement conditions recommended for dupilumab to align with those recommended for upadacitinib. There was general agreement with expanding the prescribing conditions to include other specialists to ensure equal and reasonable access to dupilumab. Although updating the initiation criteria was also viewed favourably, the Canadian Dermatology Association proposed a suggestion beyond harmonizing the criteria, namely, proposing a different place in therapy for dupilumab. The Canadian Dermatology Association and Origins Dermatology Centre noted the differences in adverse effect profiles and monitoring required, some of which could be significant, as part of concerns with off-label use of systemic immunomodulators. Conversely, input from the Dermatologist and Allergist Group Managing Atopic Dermatitis suggested adding other agents to the list of systemic immunomodulators for the patient to be treated with before initiating dupilumab.

Manufacturer Input

The manufacturer requested that the reimbursement condition for initiating dupilumab not be more restrictive than the reimbursement conditions for upadacitinib or abrocitinib. Of note, the manufacturer commented that while the reimbursement conditions for dupilumab, upadacitinib, and abrocitinib may be aligned, they should not be identical because it is important to acknowledge the evidence and differences between them. Sanofi-Aventis Canada Inc. agreed with expanding the prescriber criteria to include more specialists, and concurred that it is reasonable to provide an initial authorization for a maximum of 6 months, as is currently recommended for dupilumab, to assess response to treatment and potential

harms when initiating treatment. However, for subsequent renewal, the manufacturer requested for an extension to every 12 months.

Clinical Findings

Relevant details of clinical trials included in the 2020 review of dupilumab were included in the information collected for this request for advice. In addition to trial characteristics, baseline characteristics of patients — such as having received at least 1 prior systemic immunosuppressant (including azathioprine, cyclosporine, methotrexate, and mycophenolate) — were also reviewed.

Study 1526 included males and females between 12 and 18 years of age who had demonstrated a recent history of inadequate response to topical treatments, or for whom topicals were not advised (due to intolerance, side effects, or safety risks). The study population for the SOLO studies, the LIBERTY AD CHRONOS study, and the LIBERTY AD CAFÉ study consisted of patients aged 18 years and older. The main unique inclusion criteria for the SOLO trials required patients for whom topical treatment was inadvisable or provided inadequate treatment; this is contrary to the criteria in the LIBERTY AD CHRONOS trial that only required patients for whom topical treatment provided inadequate treatment and excluded patients who experienced important side effects to topical medications (e.g., intolerance or hypersensitivity). These inclusion and exclusion criteria in the LIBERTY AD CHRONOS trial were also reflected in criteria for the LIBERTY AD CAFÉ trial, with the additional inclusion criteria of either a history of prior cyclosporine (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. Of the total number of trial participants in the LIBERTY AD CAFÉ trial, 77.5% had received at least 1 prior systemic immunosuppressant. In the other trials where inclusion criteria did not require participants to have prior systemic immunotherapy treatments, the proportion of patients who had received at least 1 prior systemic immunosuppressant was lower. Of patients enrolled in the trials, the percentage of patients who received at least 1 prior systemic immunosuppressant ranged from 20.8% (Study 1526) to 33.6% (the LIBERTY AD CHRONOS trial).

Summary of Findings From CADTH Request for Advice Report

To reduce implementation challenges that may be faced by public drug plans, the information gathered suggests aligning the following original reimbursement conditions for dupilumab with those for upadacitinib and abrocitinib:

- Initiation criteria:
  - Patients must have had an adequate trial or be ineligible for each of the following therapies: phototherapy (where available), methotrexate, and cyclosporine.
  - Patients who have had an adequate trial of phototherapy, methotrexate, and/or cyclosporine must have documented refractory disease or intolerance.
- Prescribing conditions:
  - The patient must be under the care of a dermatologist.

CDEC Information

2020 Resubmission Meeting 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

Meeting date: March 18, 2020

Regrets: One CDEC member did not attend.

Conflicts of interest: None

2022 Request for Advice Meeting CDEC Members

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed

Meeting date: November 23, 2022

Regrets: Two CDEC members did not attend.

Conflicts of interest: None