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CADTH Reimbursement Recommendation

Dupilumab (Dupixent)

Indication: For the treatment of patients aged 6 months 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

Summary

What Is the CADTH Reimbursement Recommendation for Dupixent?

CADTH recommends that Dupixent be reimbursed by public drug plans for the treatment of patients aged 6 months to younger than 12 years 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.

The CADTH Canadian Drug Expert Committee (CDEC) recommendation for Dupixent for the treatment of patients aged 12 years and older with moderate to severe AD dated February 2023 continues to apply to patients who are not included in the population evaluated in this recommendation.

Which Patients Are Eligible for Coverage?

Dupixent should only be covered to treat patients aged 6 months to younger than 12 years with moderate to severe AD who previously tried and did not experience improvement with, or are unable to use, topically applied drugs.

What Are the Conditions for Reimbursement?

Dupixent should only be reimbursed if the patient is under the care of a dermatologist, allergist, clinical immunologist, or pediatrician who has expertise in the management of moderate to severe AD, and if the cost of Dupixent is reduced. When first prescribed, Dupixent should only be reimbursed for 6 months. Dupixent 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.

Why Did CADTH Make This Recommendation?

- In 1 clinical trial that enrolled patients aged 6 months to younger than 6 years with moderate to severe AD, and another clinical trial that enrolled patients aged 6 years to younger than 12 years with severe AD, Dupixent reduced AD severity and itching and improved health-related quality of life (HRQoL) compared to placebo.
- Dupixent may meet some needs that are important to patients, including reducing AD severity and symptoms and improving 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. A price reduction is therefore required.

Summary

- Based on public list prices, Dupixent is estimated to cost the public drug plans approximately $1,523,349,925 over the next 3 years. However, the actual budget impact is uncertain.

Additional Information

What Is AD?

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

Unmet Needs in AD

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

How Much Does Dupixent Cost?

Treatment with Dupixent is expected to cost approximately $12,723 per year for patients aged 6 months to 5 years and $25,446 per year for patients aged 6 years to 12 years.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that dupilumab be reimbursed for the treatment of patients aged 6 months to younger than 12 years 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 conditions listed in Table 1 are met.

The CDEC recommendation for dupilumab for the treatment of patients aged 12 years and older with moderate to severe AD dated February 2023 continues to apply to patients who are not included in the population evaluated in this recommendation.

Rationale for the Recommendation

Two double-blind randomized controlled trials (RCTs) (the LIBERTY AD PRESCHOOL trial, N = 162, and the LIBERTY AD PEDS trial, N = 367) evaluated the use of dupilumab in patients with AD whose disease was not adequately controlled with topical prescription therapies. The LIBERTY AD PRESCHOOL trial enrolled patients aged 6 months to younger than 6 years with moderate to severe AD, and the LIBERTY AD PEDS trial enrolled patients aged 6 years to younger than 12 years with severe AD. Both the LIBERTY AD PRESCHOOL and LIBERTY AD PEDS trials demonstrated that, compared with placebo in combination with topical corticosteroids (TCSs), 16 weeks of treatment with dupilumab in combination with TCSs was associated with statistically significant and clinically meaningful improvements in a range of outcomes that are important to patients, caregivers, and clinicians in the management of AD, including overall severity of AD (Eczema Area and Severity Index [EASI] and Investigator's Global Assessment [IGA]) response), intensity of itching (itch numeric rating scale [NRS]), and health-related quality of life (HRQoL) (Dermatitis Family Index [DFI], Children's Dermatology Life Quality Index [CDLQI], and Infants' Dermatology Quality of Life Index [IDQoL], the last of which was only assessed in the LIBERTY AD PRESCHOOL trial).

Patients and caregivers identified a need for treatment options that effectively manage the disease, improve symptoms, improve HRQoL, and are simpler to administer. CDEC concluded that dupilumab appears to address some of these needs, such as improving all disease-related symptoms (including itching and disease severity), and also meaningful improvement in HRQoL.

Using the sponsor-submitted price for dupilumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for dupilumab plus best supportive care (BSC) was $130,945 per quality-adjusted life-year (QALY) gained, compared to BSC alone. At this ICER, dupilumab is not cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold for patients aged 6 months to younger than 12 years with moderate to severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. A price reduction is required for dupilumab to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients aged 6 months to younger than 12 years with moderate to severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.	The LIBERTY AD PRESCHOOL and LIBERTY AD PEDS trials enrolled patients aged 6 months to younger than 6 years with moderate to severe AD, and 6 years to younger than 12 years with severe AD, respectively.	Based on the trials, moderate to severe AD is defined as an EASI score of 16 points or higher, or an IGA score of 3 or 4. Adequate control and refractory disease are optimally defined using similar criteria to those used in the dupilumab RCTs, such as having an EASI-75.
2. The physician must provide the EASI score and IGA score at the time of initial request for reimbursement.	The LIBERTY AD PRESCHOOL trial enrolled patients with an EASI score of 16 points or higher, and an IGA score of 3 or higher. The LIBERTY AD PEDS trial enrolled patients with an EASI score of 21 points or higher, and an IGA score of 4.	—
3. The maximum duration of initial authorization is 6 months.	Response to treatment in the pivotal trials was assessed at 16 weeks; however, the clinical experts noted to CDEC that an initial authorization period of 6 months would be reasonable, considering that AD is a chronic disease and dupilumab is expected to be a relatively long-term treatment.	—
Renewal		
4. 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.	The EASI-75 was a key secondary end point in the LIBERTY AD PRESCHOOL and LIBERTY AD PEDS trials. The clinical experts noted to CDEC that in clinical practice, the response to treatment is assessed 6 months after initiating dupilumab, then every 6 months thereafter.	—
5. The physician must provide proof of maintenance of EASI-75 response from baseline every 6 months for subsequent authorizations.		The clinical experts noted to CDEC that if a patient reaches the age of 12 years after initiating dupilumab, renewal is not contingent upon the attempt of or failure of other systemic therapy and/or phototherapy, but rather on maintaining EASI-75 response.
Prescribing		
6. 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.	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.	CDEC noted that in communities with limited access to specialists, family physicians may need to be considered by jurisdictions to prescribe dupilumab in consultation with a dermatologist,

Reimbursement condition	Reason	Implementation guidance
		allergist, clinical immunologist, or pediatrician who has expertise in the management of moderate to severe AD.
7. Dupilumab should not be used in combination with phototherapy, any immunomodulatory drugs (including biologics), or a JAK inhibitor treatment for moderate to severe AD.	There is no evidence to demonstrate a beneficial effect of dupilumab when used in combination with phototherapy or any immunomodulatory agents (biologics or JAK inhibitor treatment) for moderate to severe AD.	—
Pricing		
8. A reduction in price.	The ICER for dupilumab plus BSC is $130,945 when compared with BSC alone. A price reduction of 54% would be required for dupilumab to achieve an ICER of $50,000 per QALY gained compared to BSC alone.	—
Feasibility of adoption		
9. The feasibility of adoption of dupilumab must be addressed.	At the submitted price, the incremental budget impact of dupilumab is expected to be greater than $40 million in years 1, 2, and 3. The magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).	—

AD = atopic dermatitis; CDEC = CADTH Canadian Drug Expert Committee; EASI = Eczema Area and Severity Index; EASI-75 = improvement of 75% or greater in EASI total score; IGA = Investigator Global Assessment; JAK = Janus kinase; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

Discussion Points

- CDEC discussed that pediatric patients younger than 12 years should not be required to show nonresponse to phototherapy or systemic immunosuppressants (e.g., cyclosporine, methotrexate, azathioprine, or mycophenolate mofetil) to access dupilumab, as these are uncommon therapies for this age group in Canada. The clinical experts noted to CDEC that 12 years of age is not a clinically meaningful threshold and should not necessitate changes in clinical management. CDEC discussed that once patients reach the age of 12 years, they should not be required to try phototherapy or other systemic immunosuppressants, and if they have initiated and meet the renewal criteria for dupilumab before the age of 12 years, they should be allowed to continue using dupilumab after that.
- The clinical experts noted to CDEC that some patients may have moderate AD but an EASI score lower than 16 points. Additionally, some patients may have a low affected body surface area (BSA) but severe lesions localized to special areas (e.g., hands, feet, or scalp) that could be treated with dupilumab. CDEC discussed that there is no evidence available for this subgroup of patients.

- CDEC discussed that patients could outgrow AD presented during childhood; however, the clinical experts noted that this is less likely for patients with severe disease, other atopic comorbidities, or persistent and generalized AD. To ensure prudent use of the drug, the clinical experts suggested that a trial of increasing the time between injections once disease control is achieved, with the plan to stop dupilumab altogether, is an option to be considered between the treating physician, patient, and caregiver, although stopping the drug should not be mandated. Furthermore, CDEC discussed that patients who stop treatment after an adequate treatment response, and who subsequently experience residual and persistent disease requiring reinitiation of dupilumab, should not be required to meet the initiation criteria again before restarting treatment if they are younger than 12 years or if they have already reached the age of 12 years.
- No direct or indirect comparative evidence was available comparing dupilumab with other drugs commonly used in the treatment of AD. Both RCTs compared dupilumab with placebo. Hence, the magnitude of clinical benefit with dupilumab compared with alternative therapies, such as systemic therapies, is unknown.
- Patients identified a need for a treatment that is safe and effective. CDEC discussed that the duration of the 2 trials reviewed is not adequate to assess the long-term efficacy and safety of dupilumab.
- CDEC discussed the uncertainty in the economic analysis, specifically that in the absence of comparative evidence beyond 16 weeks for the reimbursement population, the incremental gain in QALYs with dupilumab plus BSC predicted in CADTH's reanalysis may still overestimate the incremental benefits relative to BSC alone, and further price reductions may therefore be required.
- The clinical experts noted to CDEC that the distinction between moderate and severe AD is not well defined, and categorization likely varies among physicians. Although there is a lack of data regarding the use of dupilumab in patients with moderate disease between the ages of 6 years and 12 years, CDEC discussed that there is evidence available for patients with moderate disease who are younger than 6 years and older than 12 years. In addition, the experts expect that dupilumab would likely work in these patients, similarly to patients with severe disease. They also noted that the magnitude of benefit may appear to be greater in patients with severe AD, due to these patients having a larger range for improvement compared to patients with moderate AD.

Background

AD is a chronic, relapsing, inflammatory skin condition characterized by intense itching, red and swollen skin, and rash. The condition is estimated to affect 15% to 20% of children globally, and in Canada, the lifetime prevalence of AD is up to 17% of the population. Pediatric patients with AD experience substantial symptom burden, poor sleep quality, reduced HRQoL, and frequent comorbidities. The care required for these pediatric patients can be time-consuming and interferes with day-to-day activities, leading to increased feelings of caregiver anxiety, depression, worry, and helplessness. According to the clinical experts consulted by CADTH, the goals of treatment for pediatric patients with moderate to severe AD are to reduce symptom severity and improve HRQoL with minimal adverse effects, as well as to reduce caregiver burden. Treatments

include moisturizers and topical anti-inflammatory drugs; however, these are noted as being time-consuming and can have side effects, which can lead to low compliance and refractory disease. Phototherapy and systemic immunosuppressants (off-label use) are occasionally used in patients with severe disease who do not respond to topical treatments or in addition to topical treatments, although the use of systemic immunosuppressants is uncommon in patients younger than 5 years and rare in patients younger than 2 years, as these therapies have significant limitations and intolerable adverse effects.

Dupilumab has been approved by Health Canada for the treatment of patients aged 6 months and older with moderate to severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable, and can be used with or without TCSs. Dupilumab is a recombinant human immunoglobulin G4 monoclonal antibody that inhibits interleukin (IL)-4 and IL-13. For patients aged 6 months to 11 years, the drug is available as prefilled syringes containing either 200 mg or 300 mg dupilumab for subcutaneous injection, with age-based and weight-based dosing. For pediatric patients aged 6 years to 17 years with AD, the recommended dose is 300 mg every 4 weeks (for patients weighing 15 kg to less than 30 kg), 200 mg every 2 weeks (for patients weighing 30 kg to less than 60 kg), or 300 mg every 2 weeks (for patients weighing at least 60 kg), following an initial dose of 600 mg, 400 mg, or 600 mg, respectively. For pediatric patients aged 6 months to 5 years with AD, the recommended dose is 200 mg every 4 weeks (for patients weighing 5 kg to less than 15 kg) or 300 mg every 4 weeks (for patients weighing 15 kg to less than 30 kg).

Submission History

Dupilumab has been previously reviewed 3 times by CADTH for the treatment of patients with moderate to severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable: as a new drug in 2018, as a resubmission for an expanded indication in 2020, and as a request for advice in 2022. 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 AD, 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 Janus kinase (JAK) inhibitors (upadacitinib and abrocitinib), which were recommended to be reimbursed with conditions for the treatment of AD. In February 2023, CDEC issued a recommendation that dupilumab should be reimbursed for the treatment of 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, only if conditions were met.

Dupilumab received a Notice of Compliance from Health Canada for an expansion in indication from 12 years of age and older to 6 years of age and older in February 2021, and to 6 months of age and older in April 2023. Thus, dupilumab is currently approved for the treatment of patients aged 6 months and older with moderate to severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. The current review is for a submission filed by the sponsor and focuses on the expanded age group of patients. This submission is based on new evidence (2 RCTs and 1 long-term extension study) submitted by the sponsor evaluating the use of dupilumab in patients aged 6 months to younger than 12 years with moderate to severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 2 phase III, double-blind clinical studies, in patients aged 6 months to younger than 6 years with moderate to severe AD (the LIBERTY AD PRESCHOOL trial) and patients aged 6 years to younger than 12 years with severe AD (the LIBERTY AD PEDS trial)
- patients' perspectives gathered by 3 patient groups, including the Eczema Society of Canada, the Canadian Skin Patient Alliance, and Eczéma Québec
- input from public drug plans that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with AD
- input from 1 clinician group, the Canadian Dermatology Association
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

CADTH received input from 3 patient groups: the Eczema Society of Canada, and joint input from the Canadian Skin Patient Alliance and Eczéma Québec. The inputs were provided for a previous CADTH submission for dupilumab in 2021, where the indication was for patients aged 6 years to 11 years with moderate to severe AD. No new patient input was received for the current review of dupilumab.

According to the patient groups, the symptoms of AD negatively affect individuals and their families and interfere with sleep, contribute to missed school and activities, result in psychosocial issues, and result in an increased risk of mental health problems. The groups stated that disease symptoms, quality of life, access to care, and disease management are concerns that are associated with significant psychosocial, educational, financial, and occupational burden. The authors of the joint input stated that the complex, time-consuming skin treatment routines and other associated burdens make managing the disease very challenging and exhausting. Furthermore, comorbidities associated with pediatric AD require multidisciplinary management and screening to manage the disease. Patients seek a treatment that safely and effectively manages symptoms, reduces flares, and improves the quality of life of both patients and caregivers.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts explained that current topical treatments for AD do not work for all patients, can be burdensome and have low adherence, and can have side effects, and some are expensive and not covered by insurance plans. Likewise, systemic immunosuppressants are associated with numerous adverse effects, are poorly tolerated, and require regular blood monitoring. Phototherapy can be inaccessible to patients and is often not feasible for young children.

According to the experts, dupilumab would be used as a second-line therapy after failure of an adequate trial with topical therapies (e.g., TCSs, topical calcineurin inhibitors [TCIs]) but before systemic immunosuppressants, due to their poor safety profile. Both experts believed that it would be inappropriate to require patients under the age of 12 years to show nonresponse to either phototherapy or systemic immunosuppressants before being eligible for dupilumab.

Both clinical experts indicated that patients who could receive dupilumab would be identified based on clinician examination and judgment, taking into account disease severity and inadequate response to topical therapies. They also stated that patients with severe disease that is refractory to topical treatments and has a major impact on their HRQoL are most in need of effective treatment.

The experts indicated that outcomes used in clinical trials can help to gauge treatment response but are not typically used in clinical practice, except when required by a health insurer. Instead, patient assessments are usually a combination of discussion with the patient and caregiver and examination of the skin. It was noted that patients receiving dupilumab can have a delayed response, and that it would be reasonable to assess patients for response to treatment approximately 3 months to 6 months after initiating treatment with dupilumab, and then every 6 months thereafter.

According to the experts, discontinuation of dupilumab should be considered if there is a lack of response to treatment (e.g., no improvement in rash, itch, or HRQoL) or there are intolerable adverse effects. One clinician added that patients often continue to use topical treatments alongside dupilumab, and that this would not be a reason for discontinuing treatment. Although it is possible to outgrow childhood AD, both experts explained that this is less likely for patients with severe disease, other atopic comorbidities, or persistent and generalized AD. It was suggested that a trial of increasing the time between injections once disease control

is achieved, with a plan to stop dupilumab altogether, could be an option discussed and decided on between the treating physician, patient, and caregiver, although stopping the drug should not be forced.

The experts agreed that a specialist (i.e., dermatologist) would prescribe dupilumab, and it would be initiated in a hospital or community clinical setting. In situations where there is limited access to a dermatologist or pediatric dermatologist, the experts suggested that a general pediatrician, allergist, immunologist, or a physician with training in AD could prescribe the drug.

Clinician Group Input

Clinician group input was provided by the Canadian Dermatology Association. The input provided was largely aligned with that of the clinical experts consulted by CADTH. According to the clinician group input, patients can experience long wait times before seeing a specialist while their AD remains poorly controlled. They also noted that most dermatologists in Canada are neither trained in nor comfortable with managing pediatric safety lab work in the context of systemic immunosuppression. It was highlighted in the input that dupilumab is the only systemic treatment for AD indicated for this age group and does not carry the same risk profile as traditional immunosuppressants. The clinician group stated that an ideal treatment would have a proven safety record in this age group and would also be able to reduce symptoms and improve sleep, concentration at school, and the overall quality of life for both patients and caregivers. It was also emphasized that a trial of systemic immunosuppression should not be a prerequisite for dupilumab coverage in patients aged 6 months to 5 years. The authors of the input highlighted remote Indigenous communities as being vulnerable groups in which individuals with poorly controlled AD tend to be at higher risk for chronic skin diseases and secondary infections, and that dupilumab can be a good option for patients in these communities.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for dupilumab:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Summary of Drug Plan Input and Clinical Expert Response

Implementation issues	Response
Considerations for initiation of therapy	
The reimbursement request is for treatment of patients aged 6 months to younger than 12 years with moderate to severe AD. The pivotal trials focused on 2	CDEC and the clinical expert agreed that it would be reasonable to expect that dupilumab would work similarly in patients with moderate AD as it would in those with severe AD aged 6 years to younger than 12 years old,

Implementation issues	Response
separate age groups with different disease severities. **LIBERTY AD PRESCHOOL Part B trial:** • 6 months to younger than 6 years • Moderate to severe AD • IGA > 3 • EASI ≥ 16 • BSA ≥ 10%. **LIBERTY AD PEDS trial:** • 6 years to younger than 12 years • Severe AD • IGA = 4 • EASI ≥ 21 • BSA ≥ 15%. Should there be different initiation criteria for the 2 age groups, based on the inclusion criteria for the 2 trials?	based on results from age groups both younger and older that included patients with moderate AD. The clinical experts suggest that initiation criteria should include the full moderate to severe range of severity for both age groups. The experts also noted that, in practice, patients with moderate disease can have an EASI less than 16 and could also be considered for dupilumab. They noted that these assessments consider different aspects of the disease, for example, the IGA focuses on lesion severity while the EASI varies more with BSA. The experts explained that assessments performed in clinic can consist of a balance of the severity of the lesions and how widespread the disease is. They described situations in which a patient may have a low EASI score, but could be considered for dupilumab: • More severe lesions that are not widespread (i.e., low BSA) and topicals not effective • Low BSA affected, but localized to special areas (e.g., hands, feet, scalp) based on clinical judgment and topicals are not effective.
The reimbursement request is for disease not adequately controlled with topical prescription therapies or when those therapies are not advisable, as per the Health Canada indication. What would be considered an adequate trial of topical prescription therapies?	The clinical experts noted to CDEC that an adequate trial of topical prescription therapies would include TCSs or TCIs once or twice daily for at least 4 weeks. Mild TCSs (class VI to VII) would be used on the face, while moderate (class III to V) or higher TCSs would be used on the body. According to the experts, a patient who continues to experience persistent moderate or severe dermatitis that substantially impacts their quality of life would be considered to have inadequately controlled disease.
Consider alignment with dupilumab for patients aged 12 years and older, where possible. For example: • physicians must provide the EASI score and Physician Global Assessment score at the time of the initial request for reimbursement • maximum duration of initial authorization is 6 months. If reimbursement criteria are recommended for patients aged 6 months to younger than 12 years and they do not align with CDEC-recommended initiation criteria for those aged 12 years and older (which require the use of at least 1 systemic immunosuppressant), implementation advice will be required on transitioning patients when they turn 12 years of age.	The clinical experts noted to CDEC that patients aged 6 months to younger than 12 years should not be required to try systemic immunosuppressants or phototherapy before accessing dupilumab. They also stated that 12 years of age is not a clinically meaningful threshold and should not necessitate changes in clinical management. The experts agreed that once reaching the age of 12 years, patients should not be required to try phototherapy or other systemic immunosuppressants, and that if they have initiated and are responding to dupilumab before the age of 12 years, they should be allowed to continue using dupilumab after that. Given that AD can change over time, the experts also noted to CDEC that a patient (at any age) and their caregiver can discuss with their physician if it is appropriate to stop dupilumab and see if the condition can be managed with topical therapies alone. If the patient experiences residual and persistent disease after stopping, the experts recommended that the patient restart dupilumab. The clinical experts stated that patients between the ages of 6 months and 12 years who stop dupilumab should not be required to meet the initiation criteria again before restarting treatment if they are younger than 12 years. Likewise, patients who stop dupilumab before the age of 12 years should not be required to meet the initiation criteria (including not having to try phototherapy or systemic immunosuppressants) before restarting treatment after the age of 12 years.

Implementation issues	Response
Considerations for continuation or renewal of therapy	
Consider alignment with dupilumab for patients aged at least 12 years. For example: • physicians must provide proof of beneficial clinical effect – defined as a 75% or greater improvement from baseline in the EASI score (EASI-75) 6 months after treatment initiation • physicians must provide proof of maintenance of EASI-75 response from baseline every 6 months for subsequent authorizations. Patients who are being treated with dupilumab based on any criteria recommended for the population aged 6 months to younger than 12 years may not meet the initiation criteria for those aged 12 years and older. How should these patients be assessed upon turning 12 years of age (e.g., using baseline values at initiation of treatment against renewal criteria for patients older than 12 years)?	The clinical experts stated that proof of maintenance of disease control would be an important criterion for continuing therapy and, in general, the listed continuation criteria were acceptable for patients aged 6 months to younger than 12 years. However, they were less certain if an EASI-75 would be appropriate or reasonable for all patients. They noted that some patients show meaningful improvement, but may not achieve a 75% improvement, which should not preclude them from continuing dupilumab. One expert also suggested that an initial authorization period of 6 months to 12 months would be reasonable considering that AD is a chronic disease and dupilumab is expected to be a relatively long-term treatment. As noted previously, the clinical experts stated that once a patient turns 12 years of age, they should not be required to try phototherapy or other systemic immunosuppressants to access dupilumab. One of the implementation considerations from the previous CDEC recommendation for dupilumab in patients aged 12 years and older defined moderate to severe AD based on the trials as "an EASI score of 16 points or higher, or an Investigator (Physician) Global Assessment score of 3 or 4," which the clinical experts felt was a reasonable definition. Furthermore, the clinical experts stated that continuation criteria should allow clinicians the same flexibility to use either the IGA or EASI. CDEC generally agreed with the clinical experts. CDEC also noted that assessments made every 6 months for the continuation or renewal of therapy is reasonable and that the EASI score was part of the criteria used in the previous CDEC recommendation for dupilumab. CDEC recommended to align the renewal criteria for the group aged 6 months to 12 years with that for patients who are aged at least 12 years.
Considerations for prescribing of therapy	
Is alignment with the following criteria appropriate? • 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. In specific circumstances where in some jurisdictions there is limited access to specialists (i.e., a dermatologist, allergist, clinical immunologist, or pediatrician who has expertise in the management of moderate to severe AD), could a family physician, in conjunction with a specialist, prescribe dupilumab?	The clinical experts agreed that a specialist (i.e., a dermatologist who has experience with the instruments [e.g., EASI] required to access dupilumab) would prescribe the drug. It was noted that there may be limited access to pediatric dermatologists, and general dermatologists may hesitate to prescribe dupilumab in children. However, it was noted that in those instances, a general pediatrician, allergist, immunologist, physician with training in AD, or family physician in conjunction with a specialist could prescribe the drug. CDEC recommended that 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. CDEC also noted that, in communities with limited access to specialists, family physicians with expertise in the management of moderate to severe AD might need to be considered by jurisdictions to prescribe dupilumab.
Generalizability	
The LIBERTY AD PEDS trial (with patients aged 6 years to younger than 12 years) only included patients with severe AD. Would patients with moderate AD within this age group be considered eligible for reimbursement?	The clinical experts noted to CDEC that the distinction between moderate and severe AD is not well defined and likely varies among physicians. Although there is a lack of data for dupilumab in patients with moderate disease between the ages of 6 years and 12 years, the experts expect that dupilumab would likely work in these patients similarly to patients

Implementation issues	Response
	with severe disease. They also noted that the magnitude of benefit may appear to be greater in patients with severe AD due to them having a larger range for improvement compared to patients with moderate AD.

AD = atopic dermatitis; BSA = body surface area; CDEC = CADTH Canadian Drug Expert Committee; EASI = Eczema Area and Severity Index; EASI-75 = improvement of 75% or greater in the Eczema Area and Severity Index total score; IGA = Investigator's Global Assessment; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

Clinical Evidence

Pivotal Studies and RCT Evidence

Description of Studies

Two phase III, double-blind RCTs assessed whether dupilumab with TCSs reduced a patient's IGA score to 0 or 1 compared to placebo with TCSs after 16 weeks of treatment in patients aged 6 months to younger than 6 years with moderate to severe AD (the LIBERTY AD PRESCHOOL trial, N = 162), or 6 years to younger than 12 years with severe AD (the LIBERTY AD PEDS trial, N = 367). Patients enrolled in these studies had disease that was not adequately controlled with topical prescription therapies. Key secondary outcomes included the proportion of patients with an EASI-75, percent change from baseline in EASI score, and percent change from baseline in weekly average of daily worst itch NRS score at week 16. In both studies, HRQoL outcomes were assessed as other secondary outcomes, and included the DFI, CDLQI, and IDQoL, the last of which was only assessed in the LIBERTY AD PRESCHOOL trial.

The IGA is a 5-point scale that provides a global clinical assessment of AD severity ranging from 0 (clear) to 4 (severe AD). A decrease in score relates to an improvement in signs and symptoms. The EASI is a tool used in clinical trials to assess the severity and extent of AD. For this scale, 4 disease characteristics of AD (erythema, thickness, scratching, 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 area affected by AD is assessed as a percentage by each body region and is converted to a score of 0 to 6, where the area affected 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 a higher score indicating worse disease severity. The itch NRS is a tool that patients use to report the intensity of their itch with a daily recall period. Patients 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 DFI is an AD-specific, self-administered, 10-item questionnaire designed to assess the impact of disease on the quality of life of families of children affected by disease based on a 1-week recall. Responses are scored on a 4-point Likert scale (from 0 to 3) and the total score ranges from 0 to 30, with higher scores indicating greater impairment in family quality of life. The CDLQI is a questionnaire completed by the child (aged 3 years to 16 years) designed to measure the impact of any skin disease on their quality of life with a recall period of 7 days. It consists of 10 questions asking about the impact of a skin disease on the life of the affected child, including symptoms, embarrassment, friendships, clothes, playing, sports, bullying, sleep, and impact of treatment.

Each response is rated on a 4-point Likert scale (from 0 to 3) and the total score ranges from 0 to 30, with higher scores indicating a greater degree of impairment in HRQoL. The IDQoL is a questionnaire designed to measure the impact of the skin disease on the quality of life of infants and preschool children younger than 4 years. It consists of 10 questions that examine the impact of the disease on the life of the affected child, and includes but is not limited to mood, sleep, and daily activities. Each question is rated on a 4-point Likert scale (from 0 to 3) and the total score ranges from 0 to 30, with higher scores indicating worse quality of life.

Overall, baseline patient characteristics were balanced among treatment groups in both trials. In the LIBERTY AD PRESCHOOL trial, the mean age of patients was 3.8 years, there were fewer females (38.9%) than males (61.1%), and the mean EASI score of patients was 34.1. In the LIBERTY AD PEDS trial, the mean age of patients was 8.5 years, males and females were evenly balanced, and the mean EASI score of patients was [redacted].

Efficacy Results

For the primary efficacy end point, there was a larger proportion of patients in the dupilumab group who had an IGA 0 or 1 compared to the placebo group at week 16, with a between treatment group difference of 23.8% (95% confidence interval [CI], 13.27% to 34.37%; P < 0.0001) in the LIBERTY AD PRESCHOOL trial. Results were similar in the LIBERTY AD PEDS trial, with a larger proportion of patients in both the group receiving dupilumab every 4 weeks and the group receiving dupilumab every 2 weeks who had an IGA 0 or 1 compared to the placebo group at week 16, with between treatment group differences of 21.4% (95% CI, 11.36% to 31.45%; P < 0.0001) and 18.1% (95% CI, 8.28% to 27.97%; P < 0.0001), respectively.

In the LIBERTY AD PRESCHOOL trial, a larger proportion of patients in the dupilumab group had an EASI-75 score compared to the placebo group at week 16, with a between treatment group difference of 42.3% (95% CI, 29.47% to 55.16%; P < 0.0001). Similarly, there was a larger percent change from baseline to week 16 EASI score observed in the dupilumab group compared to the placebo group, with a between treatment group least squares mean (LSM) difference of −50.4% (95% CI, −62.38% to −38.40%; P < 0.0001). Results for the proportion of patients achieving a 90% or greater improvement in the EASI total score (EASI-90) at week 16 also favoured treatment with dupilumab. In the LIBERTY AD PEDS trial, a larger proportion of patients in both the group receiving dupilumab every 4 weeks and the group receiving dupilumab every 2 weeks had an EASI-75 score compared to the placebo group at week 16, with between treatment group differences of 42.8% (95% CI, 31.54% to 54.15%; P < 0.0001) and 40.4% (95% CI, 28.95% to 51.82%; P < 0.0001), respectively. Likewise, there was a larger percent change from baseline to week 16 EASI score observed in both the group receiving dupilumab every 4 weeks and the group receiving dupilumab every 2 weeks compared to the placebo group, with between group LSM differences of −33.4% (95% CI, −40.06% to −26.82%; P < 0.0001) and −29.8% (95% CI, −36.33% to −23.24%; P < 0.0001), respectively. Results for the proportion of patients with an EASI-90 at week 16 also favoured treatment with dupilumab.

In the LIBERTY AD PRESCHOOL trial, for the itch NRS score, a larger percent change from baseline to week 16 was observed in the dupilumab group compared to the placebo group, with a between group LSM difference of −47.1% (95% CI, −59.47% to −34.79%; P < 0.0001). Results for the proportion of patients with an improvement of at least 4 points in itch NRS score from baseline to week 16 also favoured treatment with

dupilumab. In the LIBERTY AD PEDS trial, a larger percent change from baseline to week 16 was observed for the itch NRS score in both the group receiving dupilumab every 4 weeks and the group receiving dupilumab every 2 weeks compared to the placebo group, with between group LSM differences versus placebo of −28.6% (95% CI, −36.47% to −20.82%; P < 0.0001) and −31.0% (95% CI, −38.76% to −23.26%; P < 0.0001), respectively. Results for the proportion of patients achieving an improvement of at least 4 points in itch NRS score from baseline to week 16 also favoured treatment with dupilumab.

In the LIBERTY AD PRESCHOOL trial, a larger change from baseline to week 16 in the DFI score was observed in the dupilumab group compared to the placebo group, with a between group LSM difference of −7.80 (95% CI, −9.79 to −5.81; P < 0.0001). In the LIBERTY AD PEDS trial, a larger change from baseline to week 16 in the DFI score was observed in both the group receiving dupilumab every 4 weeks and the group receiving dupilumab every 2 weeks compared to the placebo group, with between group LSM differences versus placebo of [redacted] respectively.

In the LIBERTY AD PRESCHOOL trial, a larger change from baseline to week 16 in the CDLQI score was observed in the dupilumab group compared to the placebo group, with a between group LSM difference of −7.5 (95% CI, −10.29 to −4.75; P < 0.0001). In the LIBERTY AD PEDS trial, a larger change from baseline to week 16 in the CDLQI score was observed in both the group receiving dupilumab every 4 weeks and the group receiving dupilumab every 2 weeks compared to the placebo group, with between group LSM differences versus placebo [redacted] respectively.

In the LIBERTY AD PRESCHOOL trial, a larger change from baseline to week 16 in the IDQoL score was observed in the dupilumab group compared to the placebo group, with a between group LSM difference of −8.96 (95% CI, −11.71 to −6.20; P < 0.0001). This was not an outcome in the LIBERTY AD PEDS trial.

Harms Results

During the 16-week treatment period, more than half of patients in any treatment group for both trials experienced at least 1 treatment-emergent adverse event (TEAE). In the LIBERTY AD PRESCHOOL trial, 63.9% of patients in the dupilumab group and 74.4% of patients in the placebo group reported a TEAE, with the most frequently reported events being AD (13.3% with dupilumab and 32.1% with placebo), nasopharyngitis (8.4% with dupilumab and 9.0% with placebo), and upper respiratory tract infection (6.0% with dupilumab and 7.7% with placebo). In the LIBERTY AD PEDS trial, 65.0% of patients in the group receiving dupilumab every 4 weeks, 67.2% of patients in the group receiving dupilumab every 2 weeks, and 73.3% of patients in the placebo group reported a TEAE, with the most frequently reported events also being nasopharyngitis (12.5% with dupilumab every 4 weeks, 6.6% with dupilumab every 2 weeks, and 6.7% with placebo), upper respiratory tract infection (10.8% with dupilumab every 4 weeks, 8.2% with dupilumab every 2 weeks, and 10.0% with placebo), and AD (6.7% with dupilumab every 4 weeks, 8.2% with dupilumab every 2 weeks, and 14.2% with placebo).

In the LIBERTY AD PRESCHOOL trial, there were 4 patients who reported serious adverse events (SAEs) in the placebo group and 0 in the dupilumab group. In the LIBERTY AD PEDS trial, there were 2 patients who

reported SAEs in the group receiving dupilumab every 4 weeks, 0 patients in the group receiving dupilumab every 2 weeks, and 2 patients in the placebo group. No SAE was reported by more than 1 patient per trial.

In the LIBERTY AD PRESCHOOL trial, 2 patients stopped treatment because of adverse events (AEs) due to AD (dupilumab group) and nightmares (placebo group). In the LIBERTY AD PEDS trial, 4 patients stopped treatment because of AEs: 2 due to food allergy and bacterial conjunctivitis (both patients were in the group receiving dupilumab every 2 weeks) and 2 due to AD and asthma (both patients were in the placebo group).

There were no patient deaths in either trial.

Notable Harms

There were no reports of anaphylactic reaction in either trial.

There were no reports of hypersensitivity in the LIBERTY AD PRESCHOOL trial. In the LIBERTY AD PEDS trial, no treatment-related events of hypersensitivity or anaphylaxis occurred during the study.

There were no reports of helminthic infection in the LIBERTY AD PRESCHOOL trial. In the LIBERTY AD PEDS trial, [redacted] in the group receiving dupilumab every 4 weeks and the placebo group reported a helminthic infection and [redacted] in the group receiving dupilumab every 2 weeks.

In the LIBERTY AD PRESCHOOL trial, 3 patients in the dupilumab group and 0 patients in the placebo group reported conjunctivitis. In the LIBERTY AD PEDS trial, 5 patients, 7 patients, and 3 patients in the group receiving dupilumab every 4 weeks, the group receiving dupilumab every 2 weeks, and the placebo group, respectively, reported conjunctivitis.

In the LIBERTY AD PRESCHOOL trial, 2 patients in the dupilumab group and 0 patients in the placebo group reported blepharitis. In the LIBERTY AD PEDS trial, [redacted] in the group receiving dupilumab every 2 weeks and the placebo group, respectively, reported blepharitis, and [redacted] patients in the group receiving dupilumab every 4 weeks.

In the LIBERTY AD PRESCHOOL trial, [redacted] in the placebo group reported keratitis. In the LIBERTY AD PEDS trial, 1 patient in the group receiving dupilumab every 2 weeks reported keratitis, while no patients in either the group receiving dupilumab every 4 weeks or the placebo group reported keratitis.

In the LIBERTY AD PRESCHOOL trial, 2 patients in the dupilumab group and 0 patients in the placebo group reported eosinophilia. In the LIBERTY AD PEDS trial, 1 patient in the group receiving dupilumab every 2 weeks reported eosinophilia and no patients in either the group receiving dupilumab every 4 weeks or the placebo group reported this.

Facial erythema was not captured in either trial.

Injection site pain was not captured in the LIBERTY AD PRESCHOOL trial. In the LIBERTY AD PEDS trial, [redacted] in the group receiving dupilumab every 4 weeks, the group receiving dupilumab every 2 weeks, and the placebo group, respectively, reported injection site pain.

Critical Appraisal

In both pivotal trials, the few differences in baseline patient characteristics were mostly small and could have been due to chance, and the clinical experts did not think they were likely to change treatment outcomes. In the LIBERTY AD PEDS trial, 68 patients may have been unblinded to their treatment assignment, but the trial enrolled additional patients and included a modified full analysis set (mFAS) for supportive analyses to mitigate the issue. In both trials, fewer patients in the dupilumab groups used rescue treatment compared to the placebo groups, and the difference could impact how some outcomes (e.g., harms, HRQoL) are interpreted, although the direction of bias is not clear. Additionally, there was a lack of validity and reliability evidence for the itch NRS, and there were no minimal important differences (MIDs) for the IGA, DFI, or IDQoL for the patient population identified from the literature.

Although the LIBERTY AD PEDS trial included only patients with severe AD, the clinical experts were of the opinion that the results would likely be generalizable to those with moderate disease, given the evidence for age groups both younger and older than those in the trial (i.e., 6 years to younger than 12 years). The experts suggested that, in practice, a patient with moderate AD and an EASI score lower than 16 may be eligible for dupilumab if, for example, they have severe lesions but low percent BSA affected, or have lesions localized to specific areas (e.g., hands, feet, scalp). This is supported by the literature showing that patients with moderate AD can have an EASI score as low as 6. In the trials, patients who used rescue treatment were considered nonresponders, which the clinical experts stated was inconsistent with clinical practice. As per the clinical experts, non-TCS topical therapies would be acceptable add-on treatments while receiving dupilumab, and a short course (fewer than 8 weeks) of systemic therapies could be permitted without having to discontinue dupilumab. Although the trial outcomes addressed most of the treatment goals and patients' needs from the stakeholder input, it is unclear if dupilumab injections every 2 weeks or every 4 weeks meet the need for a simpler treatment, particularly if patients or their caregivers are uncomfortable with administering the injection and must receive the injections in a clinic, or if patients are especially afraid of needles.

Long-Term Extension Studies

Study 1434 is an ongoing, global, open-label, single-group, long-term extension study of patients aged 6 months to younger than 18 years with AD, with the aim to assess the long-term safety and efficacy of dupilumab. Patients who participated in the parent (pivotal) trials were eligible to enrol in Study 1434; 180 patients were from the LIBERTY AD PRESCHOOL trial and 368 were from the LIBERTY AD PEDS trial. The primary outcome was the incidence rate (events per patient-year) of TEAEs. Results presented were based on a prespecified second-step analysis conducted using data from patients aged 6 years to younger than 12 years (data cut-off date July 22, 2019) and from a third-step analysis conducted using data from patients aged 6 months to younger than 6 years (data cut-off date July 31, 2021).

Efficacy Results

At the time of this CADTH review, Study 1434 was still ongoing and no patients had completed the 260-week assessment. However, early findings from baseline, 4, 16, 28, 52, and 104 weeks of primary and secondary efficacy end points indicated that treatment effects were maintained with continued dupilumab use.

Harms Results
No new safety signals arose over the course of Study 1434 and early safety results indicated that the drug was generally well tolerated with an acceptable safety profile.

Critical Appraisal
The limited availability of long-term data (i.e., mature data), open-label design, lack of control arm, and absence of formal statistical hypothesis testing were key constraints that limit the interpretation of the long-term efficacy and safety of study outcomes for treatment with dupilumab.

Indirect Comparisons
No indirect evidence was available.

Studies Addressing Gaps in the Pivotal and RCT Evidence
The PEDISTAD study, which is an observational study, was submitted by the sponsor to address gaps in the RCT evidence comparing dupilumab to other systemic treatments, such as methotrexate or cyclosporine, for patients younger than 12 years with moderate to severe AD whose disease is not adequately controlled with topical therapies, or when those therapies are not medically advisable. The PEDISTAD study is an ongoing, international, longitudinal, 5-year, prospective study initiated on September 28, 2018, aiming to examine the impact of systemic treatments on disease severity, safety, and treatment discontinuation in this patient population. Patients were eligible to enrol if they were currently receiving systemic treatment for AD, UV therapy, or immunosuppressants, or were currently using topical treatment and would be candidates for systemic treatment. All analyses were descriptive, with no comparisons performed between different systemic treatment cohorts.

Efficacy Results
Based on findings from a 2-year interim analysis in the sponsor's Summary of Clinical Evidence, there appeared to be greater numerical improvements in the EASI total score, percent BSA affected by AD, Patient Oriented Eczema Measure score, and combined CDLQI or IDQoL score among the patients receiving dupilumab compared to methotrexate or cyclosporine.

Harms Results
Patients receiving dupilumab had a lower discontinuation rate and reported fewer AEs than those treated with methotrexate or cyclosporine.

Critical Appraisal
Based on the limited data available and how they were presented, it was not possible to determine if the treatment groups were similar enough to be compared to one another. Additionally, available data were limited to the 2-year interim results, which prevent long-term conclusions from being drawn for any outcome. There was a potential increased risk of uncontrolled confounding and selection bias in the study, no formal comparison between study groups was considered, and there was no information regarding how many patients had been lost to follow-up or how many patients were censored. The study included a small number

of patients living in Canada, and it is unclear how representative the preliminary results are to the population of pediatric patients with AD living in Canada.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree and Markov model hybrid
Target population	Patients aged 6 months to < 12 years with moderate to severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable
Treatment	Dupilumab plus BSC (topical corticosteroids and topical calcineurin inhibitors)
Dose regimen	For patients aged 6 months to 5 years, the recommended dosage of dupilumab is 200 mg or 300 mg initially, followed by 200 mg or 300 mg every 4 weeks, depending on patient weight. For patients aged 6 years to 17 years, the recommended dosage of dupilumab is 400 mg or 600 mg initially, followed by 200 mg or 300 mg every 2 weeks or every 4 weeks, depending on patient weight.
Submitted price	Dupilumab, 200 mg, 300 mg: $978.70 per prefilled syringe
Treatment cost	For patients aged 6 months to 5 years: $12,723 annually[a] For patients aged 6 years to 17 years: $26,425 in year 1 ($25,446 in subsequent years)[b]
Comparator	BSC
Perspective	Canadian publicly funded health care payer
Outcome	QALYs, LYs
Time horizon	Lifetime (100 years)
Key data source	LIBERTY AD-PRESCHOOL, LIBERTY AD-PEDS clinical trials
Key limitations	• The majority of clinical inputs used to inform the sponsor's model, including the efficacy of dupilumab beyond 16 weeks of treatment, were derived from studies involving adults. The incremental QALYs predicted with the use of dupilumab plus BSC compared to BSC alone are highly uncertain owing to the use of primarily adult data to inform the model. • The comparative efficacy and safety of dupilumab plus BSC vs. BSC alone beyond 16 weeks is highly uncertain, owing to a lack of comparative clinical data for the reimbursement population. • The efficacy of dupilumab among some subgroups is uncertain. Effectiveness of dupilumab plus BSC among patients aged 6 years to < 12 years was informed by the LIBERTY-AD PEDS trial, which enrolled patients with severe AD, and the sponsor assumed that the treatment response would be equivalent among those with moderate AD. It is unclear whether patients for whom topical therapies are not advisable are reflected in the sponsor's pharmacoeconomic analysis, owing to uncertainty in the clinical population. • Systemic therapies (such as cyclosporine-A, methotrexate, azathioprine, or mycophenolate mofetil) were not included as comparators, which was deemed inappropriate based on their use in clinical practice for the reimbursement population. • The sponsor incorporated treatment-specific utility values in their model, and patients who responded to dupilumab were assumed to have higher utility than patients who responded to BSC alone.

Component	Description
	• Utility estimates were derived from adults and may not reflect the preferences of pediatric patients. Additionally, the use of utility values from multiple sources and the programming of the sponsor's model biased the analysis in favour of dupilumab. • The savings in health care costs predicted by the sponsor with the use of dupilumab plus BSC vs. BSC alone is highly uncertain and is not supported by robust data.
CADTH reanalysis results	• In the CADTH base case, CADTH adopted alternative estimates of the durability of treatment response with BSC, health state utility values from a single study and specific to response status, and alternate estimates for costs related to health care resource use. CADTH was unable to address the lack of comparative clinical efficacy data for the reimbursement population beyond 16 weeks or the omission of systemic treatments as comparators. • Results of the CADTH base case suggest that dupilumab plus BSC is more costly (incremental costs: $118,787) and more effective (incremental QALYs: 0.91) than BSC alone, resulting in an ICER of $130,945 per QALY gained. A price reduction of 54% for dupilumab would be required for dupilumab plus BSC to be cost-effective compared to BSC alone at a willingness-to-pay threshold of $50,000 per QALY gained. • In the absence of long-term comparative clinical evidence for the reimbursement population, the CADTH reanalysis may overestimate the incremental benefits associated with dupilumab plus BSC relative to BSC alone. Further price reductions may therefore be required.

AD = atopic dermatitis; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

[a]Assumes a patient weight of 15 kg.

[b]Assumes a patient weight of 30 kg.

Budget Impact

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

- The number of patients eligible to receive dupilumab is underestimated, owing to assumptions made by the sponsor about eligibility for dupilumab that are not aligned with the Health Canada indication or requested reimbursement. Additionally, there is uncertainty in the proportion of children whose moderate to severe AD is not adequately controlled with topical prescription therapies and the proportion of children for whom topical prescription therapies are not advisable.
- The proportion of patients covered by public drug plans is likely underestimated.
- Potentially relevant comparators were excluded.
- The market uptake of dupilumab is uncertain.

CADTH reanalysis included aligning the eligibility of dupilumab with the Health Canada indication and reimbursement request, incorporating the proportion of patients eligible for public drug plan coverage, and correcting the Non-Insured Health Benefits (NIHB) and Ontario Drug Benefit (ODB) population size. CADTH reanalyses suggest that the reimbursement of dupilumab for the requested reimbursement population (patients aged 6 months to < 12 years) would be associated with a budgetary increase of $1,523,349,925 over the first 3 years (year 1: $381,570,740; year 2: $504,258,676; year 3: $637,520,510).

The estimated budget impact is highly sensitive to the number of patients eligible to receive dupilumab and the price of dupilumab.

CDEC Information

Members of the Committee

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.

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Regrets: None

Conflicts of interest: None

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Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the CADTH Drug Reimbursement Review Confidentiality Guidelines.

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