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CADTH Reimbursement Recommendation

Dupilumab (Dupixent)

Indication: As an add-on maintenance treatment in patients aged 6 years and older with severe asthma with a type 2/eosinophilic phenotype or oral corticosteroid-dependent asthma.

Sponsor: Sanofi-Aventis Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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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.

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 should be reimbursed by public drug plans for the treatment of patients aged 6 to younger than 12 years with severe asthma with a type 2/ eosinophilic phenotype if certain conditions are met.

Which Patients Are Eligible for Coverage?

Dupixent should only be covered for patients with severe asthma aged 6 to younger than 12 years with a type 2 or eosinophilic phenotype if their asthma is not controlled despite using medium- or high-dose inhaled corticosteroids (ICSs) and at least 1 additional medication or high-dose ICS alone, and if they have had at least 1 severe asthma exacerbation in the past year.

What Are the Conditions for Reimbursement?

Dupixent should only be reimbursed if prescribed by a pediatric respirologist or allergist, patients are managed by physicians with experience treating asthma in pediatric patients, and the price is reduced. Dupixent should not be used with other biologics.

Why Did CADTH Make This Recommendation?

Clinical trial evidence demonstrated that Dupixent added on to standard of care reduced the frequency of exacerbations and improved lung function compared to placebo in patients aged 6 to younger than 12 years whose asthma was uncontrolled with medium- to high-dose ICSs with at least 1 additional medication or high-dose ICS alone.

Dupixent meets some patient and caregiver needs, including improving lung function and reducing frequency of exacerbations.

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. Based on public list price and the indicated population, Dupixent may cost the public drug plans between $70 million and $84 million over the next 3 years. However, the actual budget impact is uncertain due to limitations with the submitted analysis.

Additional Information

What Is Asthma?

Asthma is a chronic lung disease that makes breathing difficult, and can be fatal in rare instances. Patients may see their physician more often, seek emergency room treatment, or become hospitalized. An estimated 14% of children aged 5 to 9 years and 19% of children aged 10 to 14 years have asthma in Canada.

Unmet Needs in Asthma

Some patients' asthma is not well controlled despite receiving other drugs; these patients can experience exacerbations that result in needing urgent medical attention or hospitalization.

How Much Does Dupixent Cost?

Treatment with Dupixent is expected to cost approximately $25,446 per patient per year for patients receiving 200 mg every 2 weeks. For those receiving 300 mg every 4 weeks, the expected cost is approximately $12,723 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that dupilumab be reimbursed as an add-on maintenance treatment in patients aged 6 to younger than 12 years with severe asthma with a type 2/eosinophilic phenotype if the conditions listed in Table 1 are met.

The CDEC recommendation for dupilumab as an add-on maintenance treatment in patients aged 12 years and older with severe asthma and with a type 2 or eosinophilic phenotype or oral corticosteroid (OCS)-dependent asthma dated June 8, 2021, continues to apply to patients who are not included in the population evaluated in the resubmission.

Rationale for the Recommendation

One double-blind, randomized controlled trial (RCT) (the VOYAGE trial, N = 408) demonstrated that, compared to placebo, treatment with dupilumab added to standard of care background therapy reduced the annualized rate of severe exacerbations and improved pulmonary function (forced expiratory volume in 1 second [FEV_1]) in patients aged 6 to younger than 12 years whose asthma remained uncontrolled with medium- to high-dose inhaled corticosteroids (ICSs). There were 2 main efficacy populations assessed in the VOYAGE trial: the type 2 inflammatory asthma phenotype population (defined as having a baseline blood eosinophil count ≥ 150 cells/μL or baseline fractional exhaled nitric oxide [FeNO] ≥ 20 pp) and the population with baseline blood eosinophils greater than or equal to 300 cells/μL. The adjusted annualized rate of severe asthma exacerbations over 52 weeks in the type 2 inflammatory asthma phenotype population was 0.305 (95% CI, 0.223 to 0.416) with dupilumab and 0.748 (95% CI, 0.542 to 1.034) with placebo, for a relative risk (RR) of 0.407 (95% CI, 0.274 to 0.605; P < 0.0001) and a risk difference (RD) [redacted] In baseline blood eosinophil count ≥ 300 cells/μL population, the adjusted rates of exacerbations were 0.235 (95% CI, 0.16 to 0.345) in the dupilumab group and 0.665 (95% CI, 0.467 to 0.949) in the placebo group (RR: 0.353; 95% CI, 0.222 to 0.562; P < 0.0001; [redacted]). The reductions in the annualized rate of severe exacerbations were statistically significant and clinically meaningful. The percent predicted pre-bronchodilator (BD) FEV_1 at week 12 increased in both the dupilumab and placebo groups in type 2 inflammatory asthma phenotype population, with a least squares (LS) mean difference (MD) between groups of 5.21% (95% CI, 2.14 to 8.27%; P = 0.0009). Similarly, the LS MD at week 12 between the dupilumab and placebo groups was 5.32% (95% CI, 1.76 to 8.88%, P = 0.0036) in the population with baseline blood eosinophil counts greater than or equal to 300 cells/μL. The changes in the percent predicted pre-BD FEV_1 were sustained through week 52 in both efficacy populations and were supportive of a clinically meaningful treatment benefit with dupilumab versus placebo.

Patients and caregivers expect new treatments for children with severe asthma to improve lung function, help manage asthma symptoms, reduce exacerbations, and reduce reliance on OCS. CDEC concluded that dupilumab meets some of these needs, including improving lung function and reducing exacerbations.

Using the sponsor-submitted price for dupilumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for dupilumab when added to standard of care background therapy was $2,999,591 per quality-adjusted life-year (QALY) compared

with standard of care background therapy alone. At this ICER, Dupixent is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for patients with severe asthma with a type 2 or eosinophilic phenotype aged 6 to younger than 12 years. 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. Dupilumab treatment should only be initiated in patients aged 6 to younger than 12 years with severe asthma with a type 2 or eosinophilic phenotype who meet all of the following criteria: 1.1. Symptoms not controlled despite optimal treatment, defined as daily use of medium- to high-dose ICS plus 1 controller medication (e.g., LABA) or high-dose ICS alone. 1.2. Eosinophil count ≥ 150 cells/μL (0.15×10^9/L). 1.3. Uncontrolled asthma with at least one severe exacerbation in the past 12 months.	The VOYAGE trial enrolled patients on medium-dose ICS with a controller medication, high-dose ICS with a controller medication, or high-dose ICS alone. Clinical experts reported that limiting chronic ICS use in children aged 6 to younger than 12 years is important. Type 2 eosinophil phenotypes are generally defined by eosinophil cell counts ≥ 150 cells/μL. The VOYAGE trial demonstrated the efficacy of dupilumab over placebo in reduced annualized rate of severe asthma exacerbations in the type 2 inflammatory population (baseline blood eosinophil count ≥ 150 cells/μL or baseline FeNO ≥ 20 ppb) and the population of patients with eosinophil cell counts ≥ 300 cells/μL. Patients enrolled in the VOYAGE trial had at least one severe exacerbation within the past year, defined as having been treated with a systemic corticosteroid, hospitalized, or having visited an emergency department for worsening asthma.	Clinical experts indicated that when managing children with severe asthma who are not well controlled on a medium-dose ICS plus another controller, they would step up to a high-dose ICS with a LABA, then consider adding a biologic. Clinical experts indicated that it would be uncommon for patients who were not controlled on high-dose ICSs alone to have a biologic added on without first adding a controller medication to their maintenance treatment. In children aged 6 to younger than 12 years old, a high-dose ICS is defined as greater than 400 mcg fluticasone propionate or equivalent daily. A severe asthma exacerbation is defined as worsening of asthma resulting in hospitalization, an emergency care visit, or treatment with systemic corticosteroids.
2. A baseline assessment of asthma symptom control using a validated asthma control questionnaire must be completed before initiation of dupilumab treatment.	A baseline assessment of asthma symptom control is needed to objectively assess response to therapy (refer to Renewal Conditions).	A validated asthma control questionnaire includes the ACQ or the ACT.
Renewal		
3. The effects of dupilumab should be assessed every 12 months to determine whether reimbursement should continue.	To allow sufficient time for patients and clinicians to assess response.	—
4. Reimbursement of dupilumab should be assessed using the same asthma control questionnaire used at	Asthma symptom control and reducing the frequency of severe asthma exacerbations were identified	Scores demonstrating a benefit of treatment for renewal of reimbursement are either of the following: a decrease

Reimbursement condition	Reason	Implementation guidance
baseline and should be discontinued if any of the following occur: 4.1. The 12-month asthma control questionnaire score has not improved from baseline, when baseline represents the initiation of treatment. 4.2. The asthma control questionnaire score achieved after the first 12 months of therapy has not been maintained subsequently. 4.3. The number of clinically significant asthma exacerbations has increased within the previous 12 months.	as important outcomes by patients, caregivers, and the clinical experts. Dupilumab reduced the annualized exacerbation rate compared with placebo in the VOYAGE trial.	of 0.5 points or more on the ACQ, or an increase of 3 or more points on the ACT. A severe asthma exacerbation is defined as worsening of asthma resulting in hospitalization, an emergency care visit, or treatment with systemic corticosteroids.
Prescribing		
5. The initial prescription of dupilumab should be by a pediatric respirologist or allergist with expertise in treating asthma. Patients should be managed by a physician with expertise in treating asthma in pediatric patients.	Specialized training is required to manage severe asthma in pediatric patients, select the appropriate treatments, and conduct testing to assess response to therapy.	—
6. Dupilumab should not be used in combination with other biologics used to treat asthma.	There is currently no evidence supporting using more than 1 biologic at the same time to improve outcomes in patients with asthma.	—
Pricing		
7. A reduction in price.	The ICER for dupilumab when added on background therapy is $2,999,591 when compared with background therapy alone. A price reduction of approximately 98% would be required for dupilumab to achieve an ICER of $50,000 per QALY compared to background therapy.	—
Feasibility of adoption		
8. The feasibility of adoption of dupilumab must be addressed.	At the submitted price, 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).	—

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; ICER = incremental cost-effectiveness ratio; ICS = inhaled corticosteroid; OCS = oral corticosteroid; LABA = long-acting beta agonist; QALY = quality-adjusted life-year.

Discussion Points

- In addition to improving lung function and reducing exacerbations, patients and caregivers indicated they want new treatments for children with severe asthma that manage asthma symptoms and reduce reliance on OCSs. In the VOYAGE trial, there was supportive evidence on the overall treatment benefit of dupilumab compared to placebo on asthma-related symptoms as measured by the Asthma Control Questionnaire (ACQ), but the differences between the groups did not exceed the minimal important difference (MID). The clinical experts noted that few pediatric patients undergo maintenance treatment with OCSs, but many may experience frequent short courses of treatment with OCSs. The VOYAGE study showed that more than 40% of patients in the placebo arm and more than 20% of patients in the dupilumab arm received at least 1 course of systemic corticosteroids. However, this outcome was not part of the statistical testing hierarchy, which precluded CDEC from drawing definitive conclusions about the effects of dupilumab on reliance on OCS in this patient population.
- CDEC discussed the safety and tolerability of dupilumab in children aged 6 to younger than 12 years. CDEC noted that there were no obvious safety or tolerability issues observed in the VOYAGE trial. Furthermore, a longer-term extension study (the EXCURSION trial, N = 365) assessing the safety and tolerability of dupilumab for an additional 52 weeks of treatment after the VOYAGE trial did not identify any new safety issues.
- No head-to-head trials have been conducted comparing dupilumab with other biologics in patients with type 2 or eosinophilic asthma. The sponsor submitted an indirect treatment comparison (ITC) that aimed to compare dupilumab to other biologics for the treatment of pediatric patients aged 6 to younger than 12 years with uncontrolled, moderate to severe asthma with a type 2 inflammatory phenotype. Findings from the sponsor-submitted ITC were inconclusive; thus, CDEC was unable to draw conclusions about the comparative clinical efficacy of dupilumab versus omalizumab in the treatment of patients who are 6 to 11 years of age with uncontrolled moderate to severe asthma. Although the VOYAGE trial did not compare dupilumab to any of the other biologics approved for the management of severe asthma in the population under review, the clinical experts consulted by CADTH reported that placebo represents an appropriate comparator because patients were not deprived of their background medication. According to the clinical experts, biologics for severe asthma have found limited use among pediatric patients in the Canadian setting at this time.

Background

Asthma is a chronic respiratory disorder characterized by reversible airway obstruction. Hallmarks of asthma include inflammation, bronchoconstriction, and airway remodelling, as well as hyperresponsive airways and mucous production. Symptoms of asthma include wheezing, dyspnea, chest tightness, sputum production, and coughing; these symptoms can be exacerbated by exogenous influences such as allergens, upper respiratory tract infections, or environmental factors such as smoke or cold air. In Canada, it is estimated that 14% of children aged 5 to 9 years and 19% of children aged 10 to 14 years suffer from asthma. According to the clinical experts consulted for this CADTH review, asthma has several diverse phenotypes, 1 of which is primarily driven by type 2 inflammation, presenting with an allergic or atopic profile and/or eosinophilic asthma.

The management of asthma is traditionally carried out using "reliever" medication for the acute relief of exacerbations, combined with controllers used on a regular or chronic basis in an effort to prevent the onset of exacerbations. Treatment of patients in Canada follows an asthma management continuum, with ICSs as the backbone of maintenance anti-inflammatory therapy, and other medications added on as necessary. Monoclonal antibodies are the newest entrants into the asthma treatment paradigm, such as IgE inhibitors, IL-5 inhibitors, and IL-4 and IL-13 inhibitors. None of the monoclonal antibodies are intended to be used first-line; rather, they are reserved for those patients whose asthma is not well controlled despite optimized controller medications.

Dupilumab has been approved by Health Canada as an add-on maintenance treatment in patients aged 6 years and older with severe asthma with a type 2 or eosinophilic phenotype or OCS-dependent asthma. Dupilumab is a monoclonal antibody that inhibits IL-4 and IL-13 signalling. It is available as a subcutaneous injection. The dosage recommended in the product monograph for children aged 6 to 11 years is 100 mg every 2 weeks or 300 mg every 4 weeks for patients with a body weight from 15 kg to less than 30 kg; 200 mg every 2 week or 300 mg every 4 weeks for patients with a body weight from 30 kg to less than 60 kg; and 200 mg every 2 weeks for patients with a body weight of 60 kg or more.

Submission History

Dupilumab has been previously reviewed by CADTH as an add-on maintenance treatment in patients aged 12 years and older with severe asthma and with a type 2 or eosinophilic phenotype or OCS-dependent asthma. In June 2021, CDEC issued a recommendation that dupilumab should be reimbursed for this indication only if conditions were met. In March 2022, 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. Thus, dupilumab is currently approved as an add-on maintenance treatment in patients aged 6 years and older with severe asthma with a type 2 or eosinophilic phenotype or OCS-dependent asthma. The current review is for a resubmission filed by the sponsor and focuses on the expanded age group of patients. This resubmission is based on new evidence (1 RCT, 1 longer-term extension study, and 1 ITC) submitted by the sponsor evaluating the use of dupilumab in patients aged 6 to younger than 12 years with asthma.

Sources of Information Used by the Committee

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

- a review of 1 RCT in patients aged 6 to younger than 12 years with asthma who were already receiving background therapy of medium-dose ICSs with a controller medication, or a high-dose ICS alone, or a high-dose ICS with a controller
- patients' perspectives gathered by 2 patient groups, Asthma Canada and the Lung Health Foundation
- input from public drug plans and cancer agencies that participate in the CADTH review process

- 2 clinical specialists with expertise diagnosing and treating patients with asthma
- input from 1 clinician group, the Canadian Thoracic Society
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Input from patients was provided by Asthma Canada, based on a survey conducted between February 2022 and March 2022, clinical practice guidelines, product monograph, not-for-profit organization websites, and research papers. More than 100 patients (92%) and caregivers (8%) across all provinces responded to the survey, with 4 patients having had experiences with dupilumab. In addition, the Lung Health Foundation (LHF) submitted patients' input based on a survey conducted between January 2021 and June 2022 with responses from 27 patients with asthma and 2 caregivers, all living in Ontario.

Even with currently available treatments, 1 in 4 respondents to the Asthma Canada survey indicated that they had poor symptom control. About 60% of respondents worried about or had a fear of exacerbations, 47% of respondents were concerned about potential hospital admissions, and 47% of respondents were concerned with missing school or work. The survey findings highlighted challenges for children with asthma, including difficulties in inhaler use techniques, difficulties with making and keeping friends due to fatigue and less energy, activity limitations, inability to attend and concentrate at school, and sleep disturbances. Patients and parents or caregivers noted several barriers to accessing health care providers (e.g., respirologists, specialized asthma clinics) including travel time and cost, missed school or work, and the financial burden of prescription refills. The LHF input from patients indicated common symptoms of asthma, such as shortness of breath (74.2%), fatigue (67.7%), cough (51.6%), and difficulties in activities of daily living such as climbing stairs (43.4%), housework (40.0%), and physical activities (40.0%). Some of the negative impacts of asthma that were highlighted by the patients included: night or early morning waking due to breathing problems (34.5%), effect on emotional well-being (37.9%), and being short-tempered or impatient with others (31.0%).

Patients and caregivers identified the following expectations for new treatment for children with severe asthma: increasing lung function, making management of symptoms easier, reducing exacerbations, and reducing reliance on OCS. Moreover, children with asthma and their parents expected to see improved day-to-day activities affecting quality of life (school attendance, sleep, energy, participation in activities), fewer health care visits including to the ED, less anxiety and panic for potential exacerbations, less time off work, and fewer financial hardships. Respondents indicated that they would like to minimize side effects of medication but would be willing to tolerate certain side effects to improve management of asthma. Decreasing frequency and easing the administration of medication was an additional priority reported by participants. Finally, it was noted that children taking dupilumab cannot be vaccinated with live vaccines, which can pose challenges for children who are not fully immunized.

Clinician Input

Input From Clinical Experts Consulted by CADTH

According to the clinical experts consulted by CADTH on this review, the needs of the majority of patients with asthma are met with current standard therapies; however, a subset of patients remains poorly controlled despite maximized pharmacological treatment and nonpharmacological interventions such as inhaler education and improved medication adherence.

In Canada, pediatric patients with uncontrolled moderate to severe type 2 inflammatory asthma have access to treatment with biologics such as anti-IgE, anti-IL5, or anti-IL4/IL13 monoclonal antibodies. Clinical experts reported that patients that would most likely benefit dupilumab treatment include individuals with moderate to severe asthma who have not achieved optimal asthma control despite conventional therapy (i.e., high-dose ICS with add-on therapy [LABA and/or LTRA] and requiring ongoing or multiple courses of systemic corticosteroids [SCS]) and presenting with clear inflammatory phenotype, as assessed by peripheral blood eosinophil levels.

According to the clinical experts consulted by CADTH, relevant outcomes to assess treatment response in children include improvements in pulmonary function testing (improvement or stabilization of FEV_1, elimination of airflow reversibility to BD), decreases in acute asthma exacerbations, improvements in symptom control, and improvements in health-related quality of life (HRQoL). The clinical experts believed that the primary factor in deciding whether to discontinue dupilumab treatment would be lack of improvement in asthma control outcomes over many months. Moreover, treatment with dupilumab should be discontinued if serious adverse events (AEs) occur (e.g., serious immune or allergic reactions, serious dermatological reactions, malignancy, and ophthalmologic AEs). Initiation of the drug should be limited to pediatric respirologists or allergy specialists with significant pediatric asthma experience.

Clinician Group Input

Input was received from 6 clinicians, on behalf of the Canadian Thoracic Society (CTS). There were no contrary views reported between the clinician group and the clinical experts consulted for this review. The clinician group indicated that children with severe asthma have limited treatment options compared to the adult population. In addition, there is a lack of effective add-on therapies in younger children with severe asthma with non–type 2 inflammation involving neutrophilic inflammation and recurrent exacerbations caused by viral respiratory infections. According to the clinician group, key outcomes in asthma management include prevention of asthma exacerbations, maximization of quality of life, symptom prevention, and maximization of exercise tolerance. Members of CTS agreed that the use of dupilumab should be restricted to patients aged 6 to 11 years with type 2 inflammation, moderate to severe asthma that is not adequately controlled on a medium-dose ICS plus LABA (or other second controller), or high-dose ICS (or OCS), and who experienced a severe exacerbation in the past year. The CTS clinicians suggested that dupilumab should be discontinued if a lack of clinically meaningful positive outcomes over an expected time frame is observed, as well as if there are any safety concerns. Assessment of pediatric patients' eligibility for biologic asthma therapy should be limited to asthma specialists (e.g., respirologists, allergists, pediatricians with a focus on childhood asthma), according to the clinician group input.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
There are a number of biologics used for severe asthma. Mepolizumab (Nucala) and Omalizumab (Xolair) may have been better comparators than placebo in the trials as they are indicated for severe asthma in patients aged 6 years and older.	Comment from the drug plans to inform CDEC deliberations.
Given the different phenotypes and treatments for severe asthma, would mepolizumab or omalizumab have been more appropriate comparators than placebo in the clinical trials?	CDEC agreed that, in the setting of severe asthma in which symptoms are not controlled despite optimal treatment (e.g., high-dose ICS or frequent OCS), mepolizumab and omalizumab would have been appropriate comparators. Although the VOYAGE trial did not compare dupilumab to any of the other biologics approved for management of asthma, the clinical experts consulted by CADTH reported that placebo represents an appropriate comparator as long as patients were not deprived of their background medication. According to the clinical experts, biologic agents targeting IgE-mediated disease (omalizumab) and decreasing eosinophilic inflammation (mepolizumab) have found limited use among pediatric patients in the Canadian setting so far. CDEC noted that the placebo control group in the VOYAGE trial may have been appropriate, considering patients received standard of care background therapy.
Considerations for initiation of therapy	
FeNO is not part of any other asthma criteria. As this was included in the primary efficacy population and requested to be included by the sponsor, would this be a consideration to include for initiation or renewal criteria?	CDEC agreed with the clinical experts, who indicated that assessment of eligibility for dupilumab treatment should be based on peripheral blood eosinophil counts, as a surrogate for type 2 inflammation. The clinicians reported that FeNO assessments are not routinely performed in clinical practice in Canada.
For dupilumab, will there be differences in the initiation criteria between the population of patients aged 6 to 11 years and those aged 12 years and older?	The scope of this review was for patients aged 6 to younger than 12 years and was based on evidence submitted by the sponsor for this specific population. Reimbursement conditions for the population evaluated in the resubmission are outlined in Table 1. The recommendation for dupilumab as an add-on maintenance treatment in patients aged 12 years and older with severe asthma and with a type 2 or eosinophilic phenotype or OCS-dependent asthma continues to apply to patients who are not included in the population evaluated in the resubmission.
Is alignment in initiation criteria for dupilumab for patients aged 12 years and older for severe asthma reviewed by CADTH appropriate? • Patient is inadequately controlled with high-dose inhaled corticosteroids, defined as ≥ 500 mcg of fluticasone	The scope of this review was for patients aged 6 to younger than 12 years and was based on evidence submitted by the sponsor for this specific population. Reimbursement conditions for the population evaluated in the resubmission are outlined in Table 1. The recommendation for dupilumab as an add-on maintenance

Implementation issues	Response
propionate or equivalent daily, and 1 or more additional asthma controller(s) (e.g., LABAs) • Patient must have an eosinophil count ≥ 150 cells/μL (0.15 × 10^9/L) or have OCS-dependent asthma. • A baseline assessment of asthma symptom control using a validated asthma control questionnaire must be completed before initiation of dupilumab treatment. If the criteria are not aligned; how will patients qualify for Dupixent when they age into the 12 years and older criteria?	treatment in patients aged 12 years and older with severe asthma and with a type 2 or eosinophilic phenotype or OCS-dependent asthma continues to apply to patients who are not included in the population evaluated in the resubmission.
Considerations for continuation or renewal of therapy	
Would alignment with dupilumab and other biologics for severe asthma reviewed by CADTH be appropriate for patients aged 12 years and older?	The scope of this review was for patients aged 6 to younger than 12 years and was based on evidence submitted by the sponsor for this specific population. Reimbursement conditions for the population evaluated in the resubmission are outlined in Table 1. The recommendation for dupilumab as an add-on maintenance treatment in patients aged 12 years and older with severe asthma and with a type 2 or eosinophilic phenotype or OCS-dependent asthma continues to apply to patients who are not included in the population evaluated in the resubmission.
Considerations for discontinuation of therapy	
Should discontinuation criteria align with dupilumab for patients aged 12 years and older and Nucala or Fasenra: • The 12-month asthma control questionnaire score has not improved from baseline, when baseline represents the initiation of treatment. • The asthma control questionnaire score achieved after the first 12 months of therapy has not been maintained subsequently. • The number of clinically significant asthma exacerbations has increased within the previous 12 months. • In patients on maintenance treatment with OCSs, there has been no decrease in the OCS dose in the first 12 months of treatment. • In patients on maintenance treatment with OCSs, the reduction in the dose of OCS achieved after the first 12 months of treatment is not maintained or improved subsequently.	The scope this review was for patients aged 6 to younger than 12 years and was based on evidence submitted by the sponsor for this specific population. Reimbursement conditions for the population evaluated in the resubmission are outlined in Table 1. The recommendation for dupilumab as an add-on maintenance treatment in patients aged 12 years and older with severe asthma and with a type 2 or eosinophilic phenotype or OCS-dependent asthma continues to apply to patients who are not included in the population evaluated in the resubmission. CDEC noted that it is uncommon for patients aged 6 to younger than 12 years to be on maintenance treatment with OCSs. However, CDEC concluded treatment with dupilumab could be discontinued in this patient population if the following criteria are met: • In patients on maintenance treatment with OCSs, there has been no decrease in the OCS dose in the first 12 months of treatment. • In patients on maintenance treatment with OCSs, the reduction in the dose of OCS achieved after the first 12 months of treatment is not maintained or improved subsequently.
Considerations for prescribing of therapy	
No evidence identified to support combination use. Combination use in this space would significantly impact cost for jurisdictions.	Comment from the drug plans to inform CDEC deliberations.
Is alignment with the following criteria appropriate? Patients should be managed by a physician with expertise in treating asthma.	CDEC agreed with the clinical experts, who indicated that treatment with dupilumab should be managed by a pediatric respirologist or allergy specialist with significant pediatric experience. In specific circumstances (i.e., the patient is stable, or

Implementation issues	Response
Dupilumab should not be used in combination with other biologics used to treat asthma.	lives in a remote area), management of asthma with dupilumab could be performed by a family physician in conjunction with an asthma specialist (e.g., linking through telehealth services).
System and economic issues	
Dupilumab as an add-on maintenance treatment in patients aged 12 years and older with severe asthma with a type 2 or eosinophilic phenotype or OCS-dependent asthma concluded without an agreement at the pan-Canadian Pharmaceutical Alliance on June 28, 2022. Nucala, Fasenra, and Xolair have agreements in place with the pCPA.	Comment from the drug plans to inform CDEC deliberations.

ER = emergency room; EOS = Eosinophils; FeNO = fractional exhaled nitric oxide; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonists; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroids; pCPA = pan-Canadian Pharmaceutical Alliance.

Clinical Evidence

Description of Studies

The VOYAGE trial is a multinational, multicentre, randomized, double-blind, placebo-controlled study that compared dupilumab to placebo in patients aged 6 to younger than 12 years with asthma who were already receiving standard of care. A total of 408 patients with persistent asthma were randomized in a 2:1 ratio, to 1 dose of dupilumab (100 mg or 200 mg) every 2 weeks, or placebo every 2 weeks, over a treatment course of 52 weeks. The primary outcome was annualized rate of severe exacerbations, while the key secondary outcome was pulmonary function measurement (i.e., change from baseline in pre-BD percent predicted FEV_1 at week 12). There were 2 main efficacy populations assessed in the trial: the type 2 inflammatory asthma phenotype population, characterized by baseline blood eosinophil counts greater than or equal to 150 cells/μL or baseline FeNO greater than or equal to 20 ppb, and the population with baseline blood eosinophils greater than or equal to 300 cells/μL.

The median age of patients included in the VOYAGE trial was 9 years (range, 6 years to 11 years). Across both efficacy populations, the majority of patients were male (range, 64.4% to 69%), white (range, 86.3% to 89.5%), and weighed more than 30 kg (range, [redacted] More than 60% of patients in the VOYAGE study had experienced 1 or 2 severe asthma exacerbations in the previous year. At baseline, FEV_1 reversibility was slightly higher in the dupilumab versus placebo group, with a mean of 21.5% (SD = 21.37) versus 15.81% (SD = 16.4) in the type 2 asthma population, and with a mean of 22.9% (SD = 23.23) versus 16.2% (SD = 15.8) in the population with baseline eosinophils greater than or equal to 300 cells/μL. Regarding ICS dosing, more than 40% of patients were on high-dose ICSs (dupilumab versus placebo: 43.2% versus 43.9% in the type 2 asthma population, and 42.3% versus 48.8% in the population with baseline blood eosinophils ≥ 300 cells/μL) and more than 50% of patients were receiving medium-dose ICSs (dupilumab versus placebo: 55.5% versus 56.1% in the type 2 population, and 56.0% versus 51.2% in the population with baseline blood eosinophils ≥ 300 cells/μL).

Efficacy Results

Mortality

In the VOYAGE trial, there were no deaths reported across the dupilumab and placebo groups.

Acute Asthma Exacerbation

The adjusted annualized rate of severe asthma exacerbations over 52 weeks in the type 2 inflammatory asthma population was 0.305 (95% CI, 0.223 to 0.416) with dupilumab and 0.748 (95% CI, 0.542 to 1.034) with placebo, for an RR of 0.407 (95% CI, 0.274 to 0.605; P < 0.0001) and an RD of [redacted] In the population with a baseline eosinophil count of at least 300 cells/µL, the adjusted rates of exacerbations were 0.235 (95% CI, 0.16 to 0.345) in the dupilumab group and 0.665 (95% CI, 0.467 to 0.949) in the placebo group (RR: 0.353; 95% CI, 0.222 to 0.562; P < 0.0001; [redacted]

RRs for the dupilumab versus placebo comparison of severe exacerbation events associated with emergency department visits or hospitalizations were [redacted] for the populations with type 2 asthma and baseline blood eosinophils greater than or equal to 300 cells/µL, respectively. [redacted]

Asthma Symptoms

Symptoms were assessed using the ACQ-7. At week 24, ACQ-7 scores decreased (improved) in both the dupilumab and placebo groups, with the LS mean (standard error [SE]): −1.33 (0.05) in the dupilumab group and −1.00 (0.07) in the placebo group, for an LS MD of −0.33 (95% CI, −0.50 to −0.16; P = 0.0001) in the type 2 population. In the population with baseline blood eosinophil counts greater than or equal to 300 cells/µL, the LS mean (SE) change from baseline to week 24 was −1.34 (0.06) with dupilumab and −0.88 (0.09) with placebo, for a difference between groups of −0.46 (95% CI, −0.67 to −0.26; P < 0.0001).

Results were maintained during the trial period (to week 52) across both efficacy populations.

Reduction in Use of Oral Corticosteroids

The proportion of patients experiencing treatment with SCS during the trial was higher in the placebo arm compared to the dupilumab arm (dupilumab versus placebo: 24.2% versus 40.4% within the type 2 inflammatory asthma phenotype and 22.3% versus 41.7% within the population with baseline blood eosinophils greater than or equal to 300 cells/µL). Adjusted relative risks in annualized SCS courses, for the comparison of dupilumab to placebo, were 0.407 (95% CI, 0.272 to 0.609) and 0.340 (95% CI, 0.212 to 0.545), within the type 2 inflammatory asthma phenotype and the population with baseline eosinophils greater than or equal to 300 cells/µL, respectively.

Pulmonary Function

The percent predicted pre-BD FEV_1 at week 12 increased in both the dupilumab and placebo groups in the type 2 inflammatory asthma phenotype population, with an LS MD between groups of 5.21% (95% CI, 2.14 to 8.27%; P = 0.0009). Similarly, an LS MD at week 12 between the dupilumab and placebo groups of 5.32% (95% CI, 1.76% to 8.88%, P = 0.0036), in the population with baseline blood eosinophil counts greater than or equal to 300 cells/µL was reported. In both primary efficacy populations, LS mean changes in the percent predicted pre-BD FEV_1 were sustained through week 52.

Reduction in Dose of ICS

The VOYAGE study protocol allowed a permanent increase in background medications after 2 or more severe asthma exacerbations. During the treatment period of the trial, [redacted].

Health-Related Quality of Life — PAQLQ

In the type 2 inflammatory asthma phenotype population in the VOYAGE trial, PAQLQ(S) scores increased (improved) from baseline to week 52, with an LS MD between the dupilumab and placebo groups of 0.34 (95% CI, 0.16 to 0.52; [redacted]). In the population with at least 300 cells/μL baseline blood eosinophils, similar differences at week 52 between groups were observed ([redacted]).

Reduction in Use of Rescue Medication

An overall decrease in number of puffs of reliever medications across the 24-hour period was observed in both treatment arms (LS MDs between the dupilumab and placebo groups at week 52 were [redacted] and [redacted] for the type 2 inflammatory asthma phenotype population and the population with baseline blood eosinophils greater than 300 cells/μL, respectively.

Harms Results

In the VOYAGE trial, AEs occurred in 83% and 79.9% of patients in the dupilumab and placebo groups, respectively. The most common AEs for dupilumab versus placebo, respectively, were: nasopharyngitis (18.5% versus 21.6%), viral upper respiratory tract infection (12.2% versus 9.7%), pharyngitis (8.9% versus 10.4%), bronchitis (6.3% versus 10.4%), allergic rhinitis (5.9% versus 11.9%), injection site erythema (12.9% versus 9.7%) and injection site edema (10.3% versus 5.2%). SAEs were reported by 4.8% of patients receiving dupilumab and 4.5% of patients receiving placebo, the majority of which were asthma (dupilumab versus placebo: 1.5% versus 0%) and eosinophilia (0.7% versus 0%). Discontinuation due to an AE occurred in 1.8% versus 1.5% of patients in the VOYAGE trial, in the dupilumab versus placebo groups, respectively.

Regarding notable harms, injection site reactions were the most commonly reported, [redacted] in the dupilumab and placebo groups, respectively. Hypersensitivity and anaphylactic reactions occurred in [redacted], respectively. In terms of infections, severe cases occurred in [redacted] in the placebo group. Parasitic infections were reported only among patients in the dupilumab group (2.6%). Eosinophilia was reported more frequently in the dupilumab arm compared to the placebo arm (5.9% versus 0.7%). More patients in the placebo group experienced conjunctivitis compared to the dupilumab group (dupilumab versus placebo: 2.6% versus 6.7% for conjunctivitis [narrow] and 3.0% versus 7.5% for conjunctivitis [broad]).

Critical Appraisal

The VOYAGE trial is a multinational, multicentre, randomized, double-blind, placebo-controlled study. The study used a matching placebo-controlled design, and patients and investigators were blinded to the study treatment assignment, but not the dosing of the injections. Potential for unblinding might have also occurred because of higher frequencies of injection site reactions and eosinophilic reactions in the dupilumab arm compared to the placebo arm. Multiplicity adjustments were implemented adequately for the analysis of severe exacerbation events during the 52-week treatment period, change from baseline in pre-BD percent

predicted FEV_1 at week 12, and change in ACQ-7-IA at week 24. Baseline characteristics were largely balanced between the groups of the study, except for FEV_1 reversibility, which was slightly higher in the dupilumab group compared to the placebo group. Clinical experts consulted by CADTH regarded the selection of specific time points for outcome assessment and their inclusion in the hierarchy (i.e., FEV_1 at week 12 and ACQ-7 at week 24) as not optimal, noting that 52-week assessments would have been more clinically relevant. Many important outcomes, such as HRQoL, exposure to OCSs, and ICS dose adjustments were not controlled for multiple comparisons. Although treatment withdrawals were higher in the dupilumab group compared to the placebo group, proportions of individuals discontinuing study treatment due to an AE were balanced across the 2 study arms. The number of study withdrawals was generally low (less than 6%) and appropriate sensitivity analyses were implemented to handle missing data for the primary and key secondary outcomes, suggesting limited impact on the validity of observed findings.

Dupilumab is indicated as add-on maintenance treatment in patients aged 6 years and older with severe asthma with a type 2 or eosinophilic phenotype or with OCS-dependent asthma. The current review focuses on the patient population aged 6 to 11 years, as dupilumab was previously reviewed by CADTH and received a positive recommendation for patients aged 12 years and older. Patients who were OCS-dependent were not included in the VOYAGE trial. The type 2 population was 1 of the main efficacy populations in the trial, defined as having baseline blood eosinophil counts greater than or equal to 150 cells/μL or baseline FeNO greater than or equal to 20 ppb, but the clinicians noted that FeNO assessments are not routinely performed in Canadian clinical practice, which represents an implementation limitation. Most of the VOYAGE trial population was white; therefore, generalizability of study findings to the population of patients in Canada may be limited in this regard. Although background medications administered in the trial were considered reflective of treatments used in Canadian practice by the clinician experts, it was not clear whether inhaler technique was checked throughout the trial. Despite this, adherence to background therapy was high across both treatment groups, and placebo responses were robust for many outcomes, suggesting that patients may have benefited from the close attention and monitoring they received in a clinical trial setting, per the clinical experts consulted by CADTH. The VOYAGE trial compared dupilumab to placebo (added on to standard of care), which represents a limitation, as comparative effectiveness and safety of dupilumab to other biologics approved for management of asthma in the pediatric population is limited to available indirect comparisons.

Indirect Comparisons

Description of Studies

The sponsor submitted 1 ITC. No published ITCs were identified after a systematic search of the literature performed by CADTH. The sponsor-submitted ITC aimed to compare dupilumab to other biologics for the treatment of pediatric patients aged 6 to younger than 12 years with uncontrolled, moderate to severe asthma with a type 2 inflammatory phenotype. After a systematic literature review and a feasibility assessment, a total [redacted] connected via placebo as a common comparator were identified as eligible. A series of pairwise Bucher ITCs were performed on various outcomes (severe exacerbations, deterioration of asthma [post hoc analysis], asthma symptoms, rescue medication use, HRQoL), comparing dupilumab (100 mg to 200 mg every 2 weeks) with IgE-inhibitor omalizumab (75 mg to 375 mg once or twice a month). Subgroup data were generated from the dupilumab trial population to match the allergic phenotype and inclusion criteria of omalizumab trials.

Efficacy Results

[redacted]

Harms Results

[redacted]

Critical Appraisal

Several limitations of the sponsor-submitted ITC were noted. There was considerable heterogeneity in study characteristics, patient populations, and outcomes assessed across the studies included in the network. Since the population of interest for the ITC was the type 2 inflammatory population, an assumption was made that the efficacy of IgE-inhibitor omalizumab would be maintained in these patients. Although there is clinical overlap between severe allergic and eosinophilic asthma according to the clinical experts, the amount of population concordance and its impact on indirect estimates could not be determined, as omalizumab trials were not designed to include an eosinophilic asthma population. In addition, it is unclear whether the placebo link for the ITC was sufficiently similar for making comparisons, since data from the VOYAGE trial suggested a robust placebo response on several outcomes assessed in the trial. In reference to the subgroup analysis, matching specific groups of patients with dupilumab to the omalizumab studies led to considerable reductions in sample size. The limited number of studies, as well as limited data available, restricted the possibility to perform meta-regression and account for differences across trials. There were no direct comparisons between treatments; therefore, the assessment of consistency was not feasible. In summary, due to various methodological limitations, no robust conclusions can be drawn about the comparative clinical efficacy of dupilumab versus omalizumab in the treatment of patients aged 6 to 11 years with uncontrolled moderate to severe asthma.

Other Relevant Evidence

Description of Studies

The EXCURSION study was an open-label, noncomparative, longer-term extension study that enrolled patients who completed the VOYAGE trial. The primary objective of the EXCURSION study was to assess long-term safety and tolerability of dupilumab. All patients received open-label treatment with dupilumab during the 52-week period. A total of 365 patients were enrolled in the EXCURSION study, of which 240 patients had been assigned to dupilumab treatment in the parent trial (dupilumab-dupilumab group) and 125 had been assigned to placebo treatment in the parent trial (placebo-dupilumab group). All patients in the EXCURSION study were receiving their background medication (ICSs with or without a second controller) as well as reliever therapy, if necessary. As of the database lock of January 17, 2022, the median duration of study was 449 days (range, 33 days to 563 days) for the dupilumab-dupilumab group and 450 days (range, 67 days to 590 days) for the placebo-dupilumab groups.

Efficacy Results

Severe Asthma Exacerbations

As of January 17, 2022, 9.1% and 9.4% of type 2 inflammatory asthma phenotype patients in the dupilumab-dupilumab and placebo-dupilumab groups, respectively, experienced a severe exacerbation event. When looking at the patients with eosinophils greater than or equal to 300 cells/μL at baseline in the parent study, [redacted] experienced an event in the dupilumab-dupilumab and placebo-dupilumab groups, respectively. The unadjusted annualized rate of severe exacerbation was 0.118 and 0.124 for the dupilumab-dupilumab and placebo-dupilumab groups, respectively (in the type 2 inflammatory asthma phenotype population). Similarly, in the subgroup with baseline eosinophils greater than 300 cells/μL, the unadjusted annualized severe exacerbation event rate was 0.120 and 0.119, for the dupilumab-dupilumab and placebo-dupilumab groups, respectively.

Pulmonary Function

At week 52, mean (SD) changes from baseline in percent predicted pre-BD FEV_1 were [redacted] for the dupilumab-dupilumab and placebo-dupilumab groups, respectively, in the type 2 inflammatory population, and [redacted] for the 2 groups, respectively, in the population with eosinophils greater than or equal to 300 cells/μL.

Harms Results

Among patients who entered the EXCURSION study from the VOYAGE study, 61.3% of patients in the dupilumab-dupilumab group and 68.0% of patients in the placebo-dupilumab group reported at least 1 AE as of the data cut-off of January 17, 2022. SAEs were experienced in 2.5% of patients in the dupilumab-dupilumab group and 0.8% in the placebo-dupilumab group. There were no deaths reported during the study period. AEs leading to discontinuation of treatment were reported by 3 patients (1.3%) in the dupilumab-dupilumab group [redacted] and no patients in the placebo-dupilumab group.

In terms of notable harms, hypersensitivity was experienced by [redacted] of patients in the dupilumab-dupilumab and placebo-dupilumab groups, respectively, [redacted] patients in dupilumab-dupilumab group and [redacted] in placebo-dupilumab group experiencing anaphylactic reaction. Other notable harms of interest reported during the LTE study period included: [redacted] conjunctivitis (4.2% versus 4.8%), [redacted] and parasitic infections (1.7% versus 1.6%).

Critical Appraisal

The EXCURSION trial provided additional data on the longer-term safety and efficacy of dupilumab relative to placebo. The validity of observed findings is limited due to the open-label and noncomparative study design. Statistical hypothesis testing was not part of the design. Furthermore, as the EXCURSION trial is a 1-year study, rare AEs might not be captured as of the data cut-off date. Given that the patients enrolled in the LTE study were originally from the VOYAGE parent study, and the eligibility criteria remained the same, it is reasonable to expect that the same limitations to generalizability are relevant to the EXCURSION study.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients aged 6 to < 12 years with severe asthma with a type 2 or eosinophilic phenotype, characterized by symptoms that are not controlled despite optimal treatment, EOS ≥ 150 or FeNO ≥ 20 or allergy driven asthma, and uncontrolled asthma having at least one severe exacerbation in the past 12 months
Treatment	Dupilumab plus background therapy
Dose regimen	The recommended dosage for dupilumab is 200 mg Q2W or 300 mg Q4W for those weighing 30 kg to less than 60 kg, and 200 mg Q2W for those weighing 60 kg or more.
Submitted price	Dupilumab 200 mg, 300 mg: $978.70 per prefilled syringe
Treatment cost	The annual cost for patients receiving dupilumab 200 mg Q2W is $25,446, while the annual cost for those receiving dupilumab 300 mg Q4W is $12,723. The annual cost of background therapy was calculated by the sponsor to be $529 per patient.
Comparator	Background therapy alone (consisting of ICS, ICS/LABA, LABA, LTRA, LAMA, theophylline, SABA)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs, number of exacerbations
Time horizon	Lifetime (up to patient age of 100 years)
Key data source	VOYAGE trial, EXCURSION trial
Key limitations	The sponsor's 5-substate economic model lacks face validity. Asthma control, defined using ACQ-5, was dichotomized with a threshold of 1.5 used to classify patients as controlled or uncontrolled. This dichotomization implies that a patient whose ACQ-5 score improved by as little as 0.01 (i.e., from 1.50 to 1.49) would be considered to have controlled asthma and would receive the utility benefit for the controlled health state (0.922) instead of that for the uncontrolled health state (0.819). The number of hospitalizations predicted by the sponsor's model is not aligned with clinical trial evidence. Both the 5- and 4-substate models overestimate the number of hospitalizations during the trial period. There is no evidence to suggest that dupilumab results in reduced hospitalizations based on the VOYAGE trial data. The assumption of increased mortality with a severe asthma exacerbation in the model implies a significant survival benefit with dupilumab that has not been shown in clinical trials. The model structure does not adequately reflect the management of asthma in clinical practice. The sponsor assumed that treatment response would be assessed after 52 weeks, with response defined as an improved exacerbation risk, and non-responders were assumed to discontinue dupilumab and receive background therapy alone. In practice, initial treatment response would be assessed earlier (e.g., after 4 to 6 weeks) based on Canadian Asthma Consensus or GINA guidelines. Clinical expert feedback also indicated that treatment response is not typically assessed in terms of exacerbation risk, as exacerbations are a distinct clinical outcome that may be infrequent and influenced by factors other than asthma control. Resource utilization costs were overestimated for moderate and severe exacerbations, leading to an overestimation in cost savings with dupilumab that did not meet face validity. Cost-effectiveness was therefore likely biased in favour of dupilumab. The sponsor's model employed poor modelling practices, was unnecessarily complex, and lacked transparency, preventing CADTH from fully validating the model and its findings. CADTH identified some

Component	Description
	errors in the model coding. The comparative clinical efficacy of dupilumab relative to other biologic treatments for severe asthma is highly uncertain. There is no direct head-to-head evidence comparing dupilumab and other biologics, and there is substantial uncertainty in the results of the sponsor's indirect treatment comparisons. There is limited evidence on the duration of the treatment effect. The sponsor assumed that the clinical effects of dupilumab on asthma exacerbations observed in 52-week trials would be maintained for up to 91 years. The comparative clinical efficacy of dupilumab relative to other biologic treatments for severe asthma in this age group is highly uncertain given the lack of head-to-head evidence comparing dupilumab and other biologics, and the substantial uncertainty in the results of the sponsor's indirect treatment comparisons. Currently, although other biologics are indicated for this age group, none are reimbursed by public drug plans for this age group.
CADTH reanalysis results	In the CADTH reanalysis, the hospitalization benefit associated with dupilumab in the child cohort was removed and QUEST hospitalization data were applied for the adult cohort; the risk of mortality with a severe exacerbation was removed; response assessment at 52 weeks was removed; and resource utilization costs were adjusted for moderate and severe exacerbations. Revisions to hospitalization benefit reduced the number of incremental QALYs, and changes to resource utilization costs reduced the total treatment costs and reduced the incremental costs of dupilumab. CADTH was unable to address the lack of head-to-head comparative clinical data vs. other biologic treatments or the uncertainty regarding long-term clinical effectiveness. Based on CADTH reanalyses, dupilumab plus background therapy remained more costly and more effective than background therapy alone: ICER = $2,999,591 per QALY (incremental costs = $209,655; incremental QALYs = 0.07). A price reduction of at least 98% would be required for dupilumab to be considered at a WTP threshold of $50,000 per QALY. Cost-effectiveness relative to other biologics could not be determined.

ACQ-5 = Asthma Control Questionnaire 5; GINA = Global Initiative for Asthma; ICER = incremental cost-effectiveness ratio; ICS = inhaled corticosteroid; ICS/LABA = inhaled corticosteroid and long-acting beta agonist; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; LY = life-year; Q2W = every 2 weeks; Q4W = every 4 weeks; QALY = quality-adjusted life-year, SABA = short-acting beta agonist.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the sponsor's estimate of the proportion of those with moderate to severe asthma may be overestimated; the sponsor did not separate incident and prevalent cases of asthma, although evidence suggests the prevalence as a percentage of the population may increase over time; the market shares of dupilumab were likely underestimated given the lack of currently available biologic treatments for the pediatric population; and the sponsor's calculation of the target population used several data sources that may not be applicable to the patient population in Canada.

Due to the high degree of uncertainty and inability to change the model structure, CADTH did not reanalyze the sponsor's budget impact analysis submission. However, CADTH conducted several scenario analyses to examine the impact of potential indication creep and increased market shares due to anticipated use. Estimates from these scenario analyses ranged from $70,155,402 to $84,185,405 based on public list prices.

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, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Peter Zed, and Mr. Morris Joseph

Meeting date: November 24, 2022

Regrets: Two expert committee members did not attend.

Conflicts of interest: None