

CADTH Reimbursement Recommendation

Dupilumab (Dupixent)

Sponsor: Sanofi Genzyme

Indication: Add-on maintenance treatment in patients aged 12 years and older with severe asthma with a type 2/eosinophilic phenotype or oral corticosteroid-dependent asthma

Final Recommendation: Reimburse with conditions

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

Summary

What is the CADTH reimbursement recommendation for Dupixent?

CADTH recommends that Dupixent (dupilumab) should be reimbursed by public drug plans for the treatment of severe asthma and with a type 2 or eosinophilic phenotype or oral corticosteroid (OCS)–dependent asthma if certain conditions are met.

What are the conditions for reimbursement?

Dupixent should only be reimbursed if the cost is reduced.

Which patients are eligible for coverage?

Dupixent should only be covered to treat patients who are inadequately controlled with high-dose inhaled corticosteroids and 1 or more additional asthma controller(s). Patients must have evidence of type 2 or eosinophilic phenotype asthma or have OCS-dependent asthma.

Why did CADTH make this recommendation?

Evidence from 3 clinical trials demonstrated that Dupixent added on to standard of care (SOC) reduced the frequency of asthma exacerbations compared with placebo. Dupixent, compared with placebo, also reduced the need for OCSs in 1 clinical trial of patients with OCS-dependent asthma. Based on public list prices, Dupixent is not considered cost-effective at a willingness to pay of \$50,000 per quality-adjusted life-year for the indicated population relative to SOC alone. A price reduction is therefore required

Key Messages

- Clinical evidence suggests that Dupixent should be reimbursed to treat patients aged 12 years and older with severe asthma and with a type 2 or eosinophilic phenotype or oral corticosteroid–dependent asthma.
- Economic evidence suggests that a 93% price reduction is needed to ensure Dupixent is cost-effective at a \$50,000 per quality-adjusted life-year threshold relative to standard of care alone.
- Cost-effectiveness versus other biologics is unknown.
- CADTH was unable to estimate the budget impact due to a high degree of uncertainty.

What is asthma?

Asthma is a disorder of the lungs that has no cure. People with asthma experience swelling and narrowing of the lung airways, making it difficult for the person to breathe. Patients with type 2 or eosinophilic asthma experience airway swelling from allergens (environmental factors such as pollen that cause the body to react), exercise, or upper respiratory tract infections. Eosinophils (a type of immune cell) are believed to contribute to the airway swelling in asthma. Patients start treatment with inhaled corticosteroids and other treatments are added on in those whose asthma is not well controlled. Patients with poorly controlled asthma despite treatment with standard medications may require regular treatment with OCSs, which are drugs associated with important side effects. Biologics (medications in the form of antibodies) are newer types of treatments added on to standard asthma medications in patients who have type 2 or eosinophilic asthma or who have OCS-dependent asthma. It is estimated that 2.4 million Canadians aged 12 years or older – or 12% of all children and 8% of adults – have asthma.

What is Dupixent?

Dupixent is approved by Health Canada 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. Biologic medication stops the effects of the protein interleukin on the eosinophilic and allergic inflammatory processes of asthma.

How much does Dupixent cost?

Treatment with Dupixent is expected to cost approximately \$24,949 per patient annually (initial year: \$25,909).

What other treatments are available for asthma?

There are other treatments available for asthma, including corticosteroids, bronchodilators, leukotriene receptor antagonists, and biologics.

Unmet needs in asthma

There remains approximately 5% to 10% of patients whose asthma is poorly controlled despite maximized drug and non-drug treatments.

How much do other treatments cost?

Other biologics for asthma cost between \$8,196 to \$49,682 annually per patient depending on the dose. SOC alone mainly consists of inhaled corticosteroids plus long-acting beta-2 agonist combinations, which cost substantially less.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that dupilumab should be reimbursed 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 only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Three multinational, double-blind, randomized controlled trials, QUEST (N = 1,902; 52 weeks), VENTURE (N = 210; 24 weeks), and Study DRI2544 (N = 465; 24 weeks), demonstrated that, compared with placebo, dupilumab treatment added on to SOC reduced the annualized rate of severe exacerbations in patients with moderate to severe asthma. In the VENTURE trial, which enrolled patients with severe asthma who required chronic use (at least 6 months) of an OCS to maintain asthma control, it was demonstrated that patients who received dupilumab experienced a greater reduction in OCS dose than those who received placebo. Patients expressed a desire for therapies that minimize the need for OCS use, and for therapies that are affordable, minimize adverse effects, and are convenient to use.

At the submitted price of \$960 per pre-filled syringe, the incremental cost-effectiveness ratio (ICER) for dupilumab plus SOC was \$721,678 per QALY compared with SOC alone. At this ICER, dupilumab is not cost-effective at a \$50,000 per QALY WTP threshold for all patients with severe uncontrolled eosinophilic asthma. There is no reliable evidence available that would justify a price premium for dupilumab compared with other biologics used to treat type 2 or eosinophilic asthma or oral corticosteroid-dependent asthma.

Implementation Guidance

1. Clinically significant asthma exacerbations are defined as worsening of asthma resulting in administration of systemic corticosteroids for at least 3 days or hospitalization.
2. A validated asthma control questionnaire includes the Asthma Control Questionnaire (ACQ) or the Asthma Control Test (ACT). The same questionnaire must be used at each assessment for reimbursement renewal as was used at the start of treatment. Scores demonstrating a benefit of treatment for renewal of reimbursement are either of the following:
 - a decrease of 0.5 points or more on the ACQ
 - an increase of 3 or more points on the ACT.
3. CDEC could not provide a recommendation for sequencing of dupilumab relative to other biologics because of limited evidence regarding the comparative efficacy of the various biologics and the effectiveness of different sequencing options. Similarly, CDEC cannot recommend that a different biologic be used to treat patients who have failed treatment with dupilumab due to a lack of evidence regarding the effectiveness in this population.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Patient is inadequately controlled with high-dose inhaled corticosteroids, defined as ≥ 500 mcg of fluticasone propionate or equivalent daily, and 1 or more additional asthma controller(s) (e.g., LABAs).	VENTURE enrolled patients on high-dose inhaled corticosteroids. QUEST and Study DRI12544 enrolled patients on moderate- to high-dose inhaled corticosteroids; however, clinical guidelines suggest maximizing inhaled corticosteroids before stepping up to biologic therapy.
2. Patient must have an eosinophil count ≥ 150 cells/ μ L (0.15×10^9 /L) or have OCS-dependent asthma.	Type 2 eosinophil phenotypes are generally defined by eosinophil cell counts ≥ 150 cells/ μ L. The QUEST and VENTURE trials demonstrated efficacy of dupilumab over placebo in reduced annualized rate of severe asthma exacerbations in the subgroup analyses of patients with elevated baseline eosinophil counts. VENTURE provided support for the reduction in annualized rate of severe asthma exacerbations with dupilumab in OCS-dependent asthma.
3. A baseline assessment of asthma symptom control using a validated asthma control questionnaire must be completed prior to initiation of dupilumab treatment.	Needed to objectively assess response to therapy (see Renewal conditions).
Renewal	
1. The effects of treatment should be assessed every 12 months to determine whether reimbursement should continue.	Allow sufficient time for patients and clinicians to assess response.
2. Reimbursement of treatment should be assessed using the same asthma control questionnaire used at baseline and should be discontinued if any of the following occur: <ul style="list-style-type: none"> • 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 OCS, there has been no decrease in the OCS dose in the first 12 months of treatment • In patients on maintenance treatment with OCS, the reduction in the dose of OCS achieved after the first 12 months of treatment is not maintained or improved subsequently 	Achieving and maintaining asthma control and reducing the frequency of severe asthma exacerbations were identified by patients as important outcomes and recommended by the clinical experts as clinically relevant and feasible to assess. Dupilumab reduced the annualized exacerbation rate compared with placebo in 3 clinical trials. Listing multiple measures provides flexibility in assessing response to treatment. Reducing the need for OCS to control asthma was determined to be a clinically important outcome for patients and clinicians. In VENTURE, dupilumab decreased OCS doses by 28%, or 7.6 mg per day, from baseline in patients with OCS-dependent asthma.
Prescribing	
1. Patients should be managed by a physician with expertise in treating asthma.	Specialized training is required to manage severe or refractory asthma, select the appropriate treatments, and conduct testing to assess response to therapy.

Reimbursement condition	Reason
2. 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	
A reduction in price	<p>The lack of direct comparative evidence and limitations with the sponsor provided ITC prevented estimating the cost-effectiveness of dupilumab compared with other biologics.</p> <p>Based on the CADTH base-case reanalysis comparing dupilumab to SOC alone, a 93% price reduction would be needed for the ICER to be less than a \$50,000 per QALY WTP threshold.</p>

ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LABA = long-acting beta agonist; OCS = oral corticosteroid; QALY = quality-adjusted life-year; WTP = willingness to pay.

Discussion Points

- No head-to-head trials have been conducted comparing dupilumab with other biologics in patients with type 2 or eosinophilic asthma. Two indirect treatment comparisons (ITCs) were submitted by the sponsor, 1 for patients with type 2 or eosinophilic asthma and the other for OCS-dependent patients. The limitations with the analyses, especially related to the limited evidence base and heterogeneity across the included studies, precluded drawing concrete conclusions about the comparative efficacy and safety of dupilumab versus other biologics.
- Dupilumab is also indicated for atopic dermatitis and chronic rhinosinusitis with nasal polyposis, which are common comorbid conditions with severe asthma. CDEC noted that dupilumab is currently the only biologic available for severe asthma that also has these other indications, which may inform patient preference and treatment convenience.

Background

Dupilumab has a Health Canada indication for 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. Dupilumab is an interleukin-4/13 inhibitor and it is available as a subcutaneous injection. The Health Canada–approved maintenance dose is either 200 mg every 2 weeks for patients with severe asthma with a type 2 or eosinophilic phenotype or 300 mg every 2 weeks for patients with OCS-dependent asthma or with comorbid moderate to severe atopic dermatitis or severe chronic rhinosinusitis with nasal polyposis.

Summary of Evidence

To make their recommendation, CDEC considered the following information:

- A systematic review of 3 double-blind randomized clinical studies in patients with moderate to severe asthma, including type 2 or eosinophilic asthma and/or OCS-dependent asthma

- Patients' perspectives gathered by patient groups: the British Columbia Lung Association and Lung Groups and the Lung Health Foundation
- Input from 1 clinical specialist with expertise diagnosing and treating patients with asthma
- Input from 1 clinician group, the Family Physician Airways Group of Canada
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Summary of Patient Input

Two patient groups, the British Columbia Lung Association and Lung Groups and the Lung Health Foundation provided input for this submission. Patient perspectives were obtained from a survey and from the experience of staff in regular contact with patients. The following is a summary of key input from the perspective of the patient groups:

- Respondents indicated shortness of breath and breathlessness as key symptoms, as well as fatigue, chest tightness, wheezing, and coughing. Asthma impacts their ability to play sports, exercise, work, travel, and participate in hobbies and leisure activities. Patients with severe asthma experience anxiety and depression, as do their caregivers.
- Patients expect new therapies will relieve symptoms, prolong life, reduce disability, stabilize lung function, and slow disease progression. They are particularly concerned about reducing exacerbations and further disease progression.
- Patients identified the adverse effects associated with chronic use of OCS as particularly problematic, and that even short-term use can cause problems such as sleep disturbances, increased risk of infection, and thromboembolism. Therefore, any strategies that would help reduce the need for OCS are important to patients.

Clinical Trials

The systematic review included 3 multinational, sponsor-funded, double-blind, randomized, placebo-controlled trials of patients with moderate to severe asthma: QUEST, VENTURE, and DRI12544. These trials compared dupilumab to placebo in patients with asthma who were already receiving SOC. QUEST was a 52-week phase III trial that randomized 1,902 adults and adolescents with moderate to severe asthma in a 2:2:1:1 ratio to 1 of 2 different doses of dupilumab (200 mg or 300 mg) every 2 weeks or matching placebo every 2 weeks. The VENTURE trial randomized 210 adults and adolescents with severe asthma and regular use of systemic steroids in the 6 months prior to screening to dupilumab 300 mg every 2 weeks or placebo. DRI12544 was a 24-week dose-ranging study that randomized adults with moderate to severe uncontrolled asthma to 1 of 4 different doses of dupilumab (dupilumab 200 mg or dupilumab 300 mg, every 2 weeks or every 4 weeks) or placebo. From the DRI12544 trial, only the 2 biweekly dose regimens that are approved in Canada are reported in this review.

Issues surrounding internal validity include the early failure of the statistical hierarchy in the QUEST analysis, which meant that many important outcomes such as the Asthma Quality of Life Questionnaire (AQLQ) and the ACQ could not be formally tested. The testing hierarchy for the DRI12544 study was developed retrospectively after a change in status from a non-pivotal to pivotal study based on a request from regulators. As a result, Health Canada decided that statistical claims beyond the primary outcome were "not permissible." None of the included studies had an active comparator. Only 1 of the included studies was 52 weeks in duration and, overall, the studies were unlikely to be of sufficient duration to assess the longer-term efficacy, safety, and tolerability of dupilumab. Placebo responses were robust for many of the outcomes across the trials, suggesting that patients may have benefited from

the extra training and care they received in a clinical trial setting. Study withdrawals were low across studies with no clear differences between the dupilumab and placebo groups, ranging between 4.4% and 6.5% of patients in the QUEST study, zero to 1.0% in the VENTURE study, and 4.7% and 7.0% in the DRI12544 study, respectively.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, CDEC discussed the following: annualized rate of severe exacerbations, reduction of OCS dose, health-related quality of life, asthma control, and forced expiratory volume in 1 second (FEV₁).

The co-primary outcome in the QUEST study was annualized rate of severe asthma exacerbations and change from baseline to week 12 in FEV₁. In the VENTURE study, the primary outcome was the percent reduction in OCS dose; in the DRI12544 study, it was the change from baseline to week 12 in FEV₁.

Efficacy

There were statistically significant reductions in the annualized rate of severe exacerbations for each of the dupilumab 200 mg and 300 mg doses versus placebo in the included studies. In the QUEST study, at the dupilumab 200 mg dose, the annualized rate of severe asthma exacerbations was 0.456 with dupilumab versus 0.871 for placebo, with a relative risk of 0.523 (95% CI, 0.413 to 0.662; P < 0.0001); for dupilumab 300 mg, it was 0.524 versus 0.970 for placebo, with a relative risk of 0.540 (95% CI, 0.430 to 0.680; P < 0.0001). Similar results were seen in the VENTURE study, the annualized rate of severe asthma exacerbations was 0.649 (95% CI, 0.442 to 0.955) in the dupilumab 300 mg group and 1.597 (95% CI, 1.248 to 2.043) in the placebo group, for a relative risk versus placebo of 0.407 (95% CI, 0.263 to 0.630; P < 0.0001). Similar results were also seen in the DRI12544 study, in which severe exacerbations were a secondary outcome, with a relative risk versus placebo of 0.300 (95% CI, 0.159 to 0.565; P = 0.0002) in the dupilumab 200 mg dose group and of 0.295 (95% CI, 0.159 to 0.546; P = 0.0001) in the 300 mg dose dupilumab group.

In the VENTURE study, the percent reduction in OCS dose least squares mean (LSM) difference between groups was 28.24% (95% CI, 15.81% to 40.67%; P < 0.0001). The absolute reduction in OCS dose was a LSM of 7.58 (SE = 0.58) mg/day with dupilumab 300 mg and 4.77 (SE = 0.54) mg/day with placebo, for a LSM difference between groups of 2.81 mg/day (95% CI, 1.33 to 4.29 mg/day; P = 0.0002). The clinical expert consulted by CADTH on this review believed this to be a clinically significant reduction in OCS dose. A secondary outcome of the VENTURE study was the proportion of patients with a 50% or greater reduction in OCS dose compared with baseline, and at week 24 this had been achieved by 81.0% of dupilumab 300 mg patients and 53.3% of placebo patients, for an odds ratio of 3.98 (95% CI, 2.06 to 7.67; P < 0.0001). Another secondary outcome was the proportion of patients who achieved a reduction of OCS dose to less than 5 mg/day at week 24; by week 24, these were 72.9% with dupilumab 300 mg and 37.4% with placebo, for an odds ratio of 4.48 (95% CI, 2.39 to 8.39; P < 0.0001). An "other" secondary outcome was the proportion of patients who no longer required OCS at week 24; for dupilumab 300 mg, this was 48% and for placebo it was 25%, for an odds ratio of 2.74 (95% CI, 1.47 to 5.10).

AQLQ global scores were increased (improved) across all studies. In the QUEST and DRI12544 studies, the LSM difference between dupilumab 200 mg and placebo after 24 weeks was 0.20 and 0.31, respectively, and between dupilumab 300 mg and placebo the LSM

difference was 0.15 and 0.36, respectively. In the VENTURE study, after 24 weeks the LSM difference between dupilumab 300 mg and placebo was 0.35. Results for this outcome were tested outside of the statistical hierarchy, and none of the differences between dupilumab and placebo met the minimal important difference (MID) of 0.5 for this instrument.

The ACQ-5 item score was reduced (improved) from baseline to week 24 in both the dupilumab and placebo groups across the studies. In the QUEST and DRI12544 studies, the LSM difference between dupilumab 200 mg and placebo was -0.35 in both studies, and between dupilumab 300 mg and placebo was -0.19 and -0.31 , respectively. In the VENTURE study, the LSM difference between dupilumab 300 mg and placebo after 24 weeks was -0.47 . Results for this outcome were tested outside of the statistical hierarchy and none of the differences between dupilumab and placebo met the MID of 0.5 for this instrument.

Across the studies, the difference in pre-bronchodilator FEV₁ between dupilumab and placebo at 12 weeks ranged between 0.13 L and 0.22 L, and statistically significant improvements for dupilumab over placebo were reported for both the dupilumab 200 mg and 300 mg doses. Results for this outcome in VENTURE were tested outside of the statistical hierarchy. The minimal patient perceivable improvement for FEV₁ was 0.23 L and is lower in older patients (0.17 L) than in younger patients (0.28 L).

Harms (Safety)

Overall adverse events and serious adverse events were similar across trials for dupilumab compared with placebo.

Notable harms included anaphylactic reactions, which occurred very infrequently ($< 1\%$ of patients treated with dupilumab), and serious or severe infections, which occurred more frequently with dupilumab than with placebo in some studies but not in others. Opportunistic infections were also infrequent, occurring in less than 1% of patients, and there was no indication of an increased risk with dupilumab.

Indirect Evidence

Indirect evidence comparing the efficacy of dupilumab to other monoclonal antibodies for asthma was available from 2 sponsor-submitted ITCs as well as 5 published ITCs. However, a variety of methodological issues, including the limited evidence base and clinical heterogeneity, limit any conclusions that can be drawn from this data.

Cost and Cost-Effectiveness

The annual per-patient drug acquisition cost of dupilumab (for both strengths) is \$24,949 (initial year: \$25,909) based on a unit cost of \$959.60 per syringe.

The sponsor submitted a cost-utility analysis comparing dupilumab plus background therapy to background therapy alone in patients with a type 2 or eosinophilic phenotype or OCS-dependent asthma. The sponsor's analysis was conducted from the perspective of a Canadian publicly funded health care payer over a lifetime time horizon. The sponsor submitted 2 Markov models (5-substate model; 4-substate model), which were used for analyses involving type 2 or eosinophilic asthma and OCS-dependent asthma, respectively. The 5-substate model included health states based on asthma control (controlled,

uncontrolled; defined based on ACQ-5 score), as well as states related to asthma exacerbations (moderate or severe), while the 4-substate model included health states related to asthma exacerbations (none, moderate, severe) without further breakdown by asthma control. Movement between model states was based on the QUEST trial for patients with type 2 or eosinophilic asthma and on the VENTURE trial for patients with OCS-dependent asthma. Scenario analyses compared dupilumab with other funded biologics for asthma using a network meta-analysis. The time horizon in the base case was 52 years to capture the maximum lifetime of a patient with a modelled starting age of 48 and with a 1.5% annual discount rate for costs and effects and a 4-week cycle length.

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

- The sponsor's 5-substate model lacks face validity because asthma control was dichotomized as controlled or uncontrolled, with a cut-off of 1.5 points. As such, patients who had a small improvement in ACQ score (i.e., from 1.49 to 1.50) were considered to have controlled asthma and received the utility benefit for the controlled health state instead of that for the uncontrolled health state.
- The number of exacerbations predicted by the sponsor's model was not aligned with clinical trial evidence (lacking face validity).
- The comparative clinical efficacy of dupilumab relative to other biologic treatments for severe asthma is highly uncertain due to the lack of any direct head-to-head evidence and limitations with the submitted NMA.
- For a condition that is managed over the patient's lifetime, there is limited evidence of the duration of treatment effect beyond the clinical trial which lasted 1 year.
- The sponsor's assumption of increased mortality with a severe asthma exacerbation 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, in terms of both the timing and definition of treatment response.
- The sponsor's model employed poor modelling practices, was unnecessarily complex, and lacked transparency.
- The cost-effectiveness of dupilumab among adolescents is uncertain because the analyses were based on adult patients and the clinical trials on which the effectiveness and utility values were based enrolled predominantly adult patients.
- The cost-effectiveness of the 300 mg strength of dupilumab is uncertain because the sponsor's submitted analysis incorporated data based solely on the 200 mg arm of the QUEST trial.

CADTH undertook reanalyses for the type 2 or eosinophilic population to address the identified limitations (i.e., aligning the relative risk of severe asthma exacerbations with the QUEST trial, assuming no mortality benefit associated with dupilumab, and removing the response assessment at 52 weeks). CADTH could not address several limitations with the sponsor's submission, including the lack of head-to-head comparative clinical data, uncertainty regarding long-term clinical effectiveness, lack of data related to the 300 mg strength, and a lack of data for adolescents. CADTH could not fully validate the sponsor's model because of a lack of transparency and poor modelling practices. Based on CADTH reanalyses, dupilumab is not cost-effective at a \$50,000 WTP threshold at an ICER \$721,678 per QALY gained compared with background therapy. A price reduction of 93% would be

required for dupilumab to be considered optimal at a WTP threshold of \$50,000 per QALY. CADTH was unable to determine the cost-effectiveness of dupilumab relative to other currently available biologics. Finally, the ICER for patients who were OCS-dependent was found to be \$425,333 per QALY; however, this result is highly uncertain.

Members of the Canadian Drug Expert Committee

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

Meeting date: April 21, 2021

Regrets: One expert committee member did not attend.

Conflicts of interest: None