CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Dupilumab (Dupixent)

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

Recommendation: Reimburse with Conditions

Version:	1.0
Publication Date:	May 2021
Report Length:	10 Pages

Single Technology

DUPILUMAB (DUPIXENT — SANOFI GENZYME)

Therapeutic Area: Severe eosinophilic asthma

Recommendation

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

Rationale for the Recommendation

Three multinational, double-blind, randomized controlled trials (RCTs), 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 standard of care (SOC) reduced the annualized rate of severe exacerbations in patients with type 2 eosinophilic asthma. In VENTURE, which enrolled patients with severe eosinophilic asthma who required chronic use (at least six months) of an oral corticosteroid (OCS) to maintain asthma control, it was demonstrated that patients receiving dupilumab experienced a greater reduction in OCS dose than with placebo. Patients expressed a desire for therapies that minimize the need for OCS use, and for therapies that are affordable, minimize adverse effects and 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 quality-adjusted life-year (QALY) compared with SOC alone. At this ICER, dupilumab is not cost-effective at a $50,000 per QALY willingness to pay (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 eosinophilic asthma.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason
Initiation	
1. Patient is inadequately controlled with high-dose inhaled corticosteroids, defined as greater or equal to 500 mcg of fluticasone propionate or equivalent daily, and one 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/μL or have OCS-dependent asthma	Type 2 eosinophil phenotypes are generally defined by eosinophil cell counts ≥ 150 cells/μL. The QUEST and VENTURE trials demonstrated efficacy of dupilimab over placebo in reduced annualized rate of severe asthma exacerbations in the subgroup analyses of patients with elevated baseline eosinophil counts. VENTURE provides support for the reduction in annualized rate of severe asthma exacerbations of 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: 2.1. the 12 month asthma control questionnaire score has not improved from baseline, when baseline represents the initiation of treatment, or 2.2. the asthma control questionnaire score achieved after the first 12 months of therapy has not been maintained subsequently, or 2.3. the number of clinically significant asthma exacerbations has increased within the previous 12 months, or 2.4. in patients on maintenance treatment with OCS, there has been no decrease in the OCS dose in the first 12 months of treatment, or 2.5. 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 three 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.

Reimbursement Condition	Reason
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.
2. Dupilumab should not be used in combination with other biologics used to treat asthma.	There is currently no evidence supporting using more than one biologic at the same time to improve outcomes in patients with asthma.
Pricing	
A reduction in price	Based on the CADTH base case reanalysis, a 93% price reduction would be needed for the ICER to be below a $50,000 per QALY WTP threshold. The lack of direct comparative evidence and limitations with the sponsor provided ITC prevented estimating the cost-effectiveness of dupilumab compared to other biologics.

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

Implementation Guidance

1. Clinically significant asthma exacerbations are defined as worsening of asthma resulting in administration of systemic corticosteroids for at least three 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:
   a. a decrease of 0.5 points or more on the ACQ, or
   b. an increase of three or more points in 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 type of population.

Discussion Points

- No head-to-head trials have been conducted comparing dupilumab with other biologics in patients with type 2 eosinophilic asthma. Two indirect treatment comparisons (ITCs) were submitted by the sponsor, one in patients with type 2 eosinophilic asthma and the other in 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 an older with severe asthma with a Type 2/eosinophilic phenotype or OCS-dependent asthma. Dupilumab is an interleukin(IL)-4/13 inhibitor and it is available as a subcutaneous injection. The Health Canada–approved maintenance dose is either 200mg every two weeks for patients with severe asthma with a Type 2/eosinophilic phenotype or 300mg every two weeks for patients with OCS-dependent asthma or with co-morbid 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 three double-blind randomized clinical studies in patients with type 2 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 one clinical specialist with expertise diagnosing and treating patients with asthma
- Input from one 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 & Lung Groups (BCLG) and the Lung Health Foundation (LHF) 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 the 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 three 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 standard of care. QUEST was a 52 week Phase 3 trial that randomized 1902 adults and adolescents with moderate to severe asthma in a 2:2:1:1 ratio to one of two different doses of dupilumab (200mg or 300mg) every two weeks or matching placebo every two weeks. VENTURE randomized 210 adults and adolescents with severe asthma and regular use of systemic steroids in the six months prior to screening to dupilumab 300mg every 2 weeks or placebo. DRI12544 was a 24 week dose ranging study that randomized adults with moderate to severe uncontrolled asthma to one of four different doses of dupilumab (dupilumab 200mg or dupilumab 300mg, every two weeks or every four weeks) or placebo. From the DRI12544, only the two biweekly dose regimens that are approved in Canada are reported in this review.

Issues surrounding internal validity include the fact that early failure of the statistical hierarchy in QUEST analysis meant that many important outcomes such as the Asthma Quality of Life Questionnaire (AQLQ) and the Asthma control Questionnaire (ACQ) could not be formally tested. The testing hierarchy for DRI12544 was developed retrospectively, after a change in status from non-pivotal to pivotal study based on a request from regulators. As a result of this, Health Canada decided that statistical claims beyond the primary outcome were 'not permissible'. None of the included studies had an active comparator. Only one 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 benefitted from the extra training and care they received in a clinical trial setting. Study withdrawals were low across studies with no clear differences between groups, ranging between 4.4% and 6.5% of patients in QUEST, zero to 1.0% in VENTURE, and 4.7% and 7.0% in DRI12544.

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

Efficacy

There were statistically significant reductions in annualized rate of severe exacerbations for each of the dupilumab 200mg and 300mg doses versus placebo in the included studies. In QUEST, at the dupilumab 200 mg dose, the annualized rate of severe asthma exacerbations was 0.456 with dupilumab versus 0.871 placebo, for a relative risk of 0.523 [95% CI: 0.413, 0.662], p<0.0001 and for dupilumab 300mg it was 0.524 versus 0.970 placebo, relative risk of 0.540 [95% CI: 0.430, 0.680], p<0.0001. Similar results were seen in VENTURE, in the dupilumab 300 mg group, 0.649 [95% CI: 0.442, 0.0955] and 1.597 in the placebo group [95% CI: 1.248, 2.043], for a relative risk versus placebo of 0.407 [95% CI: 0.263, 0.630], p<0.0001. Similar results were also seen in the DRI12544 study, where severe exacerbations were a secondary outcome, with a relative risk versus placebo in the dupilumab 200 mg dose group of 0.300 [95% CI: 0.159, 0.565], p=0.0002 and in the 300 mg dose dupilumab group of 0.295 [95% CI: 0.159, 0.546], p=0.0001.

In VENTURE, the percent reduction in OCS dose, LSM difference between groups was 28.24% [95% CI: 15.81, 40.67], p<0.0001. The absolute reduction in OCS dose was a LSM (SE) of 7.58 mg/day (0.58) with dupilumab 300 mg and 4.77 mg/day (0.54) with placebo, for a LSM difference between groups of 2.81 mg/day [95% CI: 1.33, 4.29], 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 VENTURE was the proportion of patients with a 50% or greater reduction in OCS dose compared to 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, 7.67], p<0.0001. The proportion of patients achieving a reduction of OCS dose to <5mg/day at week 24 was another secondary outcome, and by week 24 there were 72.9% with dupilumab 300 mg and 37.4% with placebo, for an odds ratio of 4.48 [95% CI: 2.39, 8.39], p<0.0001. An 'other' secondary outcome was the proportion of patients no longer requiring OCS at week 24, and with dupilumab 300 mg this was 48% and placebo 25%, for an odds ratio of 2.74 [95% CI: 1.47, 5.10].

AQLQ global scores were increased (improved) across all studies. In QUEST and DRI12544, 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 was 0.15 and 0.36, respectively. In VENTURE, 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 MID of 0.5 for this instrument.

The ACQ-5 item score was reduced (improved) from baseline to week 24 in each of the dupilumab and placebo groups across the studies. In QUEST and DRI12544, 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 VENTURE, 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 litres and 0.22 litres, 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 (MPPI) for FEV1 is 0.23 litres and is lower in older patients (0.17 litres) than in younger patients (0.28 litres).

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 numerically more frequently with dupilumab than with placebo in some studies but not in others. Opportunistic infections were also infrequent, occurring in <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 two sponsor-submitted ITCs as well as five 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/eosinophilic phenotype or OCS-dependent asthma. The sponsor's analysis was conducted from the perspective of a Canadian publicly funded healthcare payer over a lifetime time horizon. The sponsor submitted two Markov models (5-sub-state model; 4-sub-state model), which were used for analyses involving type 2/eosinophilic asthma and OCS-dependent asthma, respectively. The 5-sub-state model included health states based on asthma control (controlled, uncontrolled; defined based on Asthma Control Questionnaire [ACQ-5] score), as well as states related to asthma exacerbations (moderate or severe), while the 4-sub-state 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/eosinophilic asthma and on the VENTURE trial for patients with OCS-dependent asthma. Scenario analyses compared dupilumab to 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 patients with a modelled starting age of 48, 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-sub-state model lacks face validity, in that 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 one 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 modeling practices, was unnecessarily complex, and lacked transparency.
- The cost-effectiveness of dupilumab among adolescents is uncertain, as the analyses were based on adult patients, and the clinical trials on which the effectiveness and utility values are based enrolled predominantly adult patients.
- The cost-effectiveness of the 300 mg strength of dupilumab is uncertain, as 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/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 owing to a lack of transparency and poor modeling practices. Based on CADTH re-analyses, dupilumab is not cost effective at a $50,000 WTP threshold at an ICER $721,678 per QALY gained compared to 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.

CDEC Members

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.

April 21, 2021 Meeting

Regrets

One expert committee member did not attend.

Conflicts of Interest

None

CADTH

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