CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

DUPILUMAB (Dupixent)

Sanofi-aventis Canada Inc.

Indication: Add-on maintenance treatment in adult patients with uncontrolled chronic obstructive pulmonary disease (COPD) associated with type 2 inflammation.

December 20, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CADTH and do not necessarily represent or reflect the views of CADTH. No endorsement by CADTH is intended or should be inferred.

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CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0878-000
Generic Drug Name (Brand Name): Dupilumab
Indication: Add on therapy for COPD management in patients at high risk for COPD exacerbations
Name of Clinician Group: Canadian Thoracic Society
Author of Submission: David Gourde, Dr. Joshua Wald, Dr. Erika Penz, Dr. Imran Satia, Dr. Tony D'urzo, on behalf of the COPD Assembly, Canadian Thoracic Society

1. About Your Clinician Group

Canadian Thoracic Society (CTS) is the national inter-disciplinary specialty society for respirology, bringing together physicians, scientists and healthcare professionals from a variety of disciplines working in respiratory health and research.

CTS promotes lung health by enhancing the ability of healthcare professionals through leadership, collaboration, research, learning and advocacy, and providing the best respiratory practices in Canada. The work of the CTS is largely carried out by its members who serve on a voluntary basis in a diverse range of committees encompassing clinical interests, membership services and communications, continuing professional development, research, development of evidence-based guidelines and knowledge translation, in the area of pediatric and adult respiratory medicine. The leadership role that CTS members play in clinical practice and research confers a very high profile and recognition at national and international levels. The CTS is recognized as an accrediting body of the Royal College of Physicians and Surgeons for specialist education and continuing professional development.

Website: https://cts-sct.ca/

2. Information Gathering

The following document has been prepared as a submission to CADTH in response to its request for clinician input into the application by Sanofi Canada regarding the approval of DUPIXENT™ for add on therapy in selected patients with COPD. This document represents the opinion of the Canadian Thoracic Society with respect to the use of this medication in adults with COPD. Joshua Wald and David Gourde, Co-Chairs of the CTS COPD Assembly Steering Committee, and Erika Penz, President-elect of the CTS prepared the initial draft of this document. The draft was sent to members of the CTS COPD Assembly (Madeleine Warwick, Shirley Quach, Imran Satia, Alina Blazer, Meyer Balter, Anthony D'Urzo) for comments and review. The final draft document was then submitted to the CTS Executive Committee for review, revision and approval prior to its submission.

3. Current Treatments and Treatment Goals

The key goals of treatment for COPD are to improve symptoms and health status, to reduce exacerbations, and to reduce mortality. These goals can also be divided into two broad categories: reducing symptoms and reducing future risk. Reducing symptoms includes relieving dyspnea, wheeze, cough and phlegm, improving overall health status and quality of life, and improving exercise tolerance. Reducing future risk includes preventing disease progression, preventing and treating exacerbations and reducing mortality.

Non-drug therapies recommended for patients with COPD include smoking cessation interventions for patients who smoke, pulmonary rehabilitation, and vaccination against respiratory infections such as influenza, COVID-19, RSV, and invasive pneumococcal disease.

Neuromuscular electrical stimulation, chest wall vibration, walking aids and pursed-lip breathing are also recommended in the management of dyspnea in the individual patient with advanced COPD.

Oxygen is recommended for COPD patients with resting hypoxemia, exertional or nocturnal hypoxemia, based on specific testing criteria.

Non-invasive ventilation: Bi-level positive airway pressure ventilation is suggested for COPD patients with evidence of chronic hypercapnia.

Surgical therapies: Lung volume reduction procedures including endobronchial valve placements, lung volume reduction surgeries and lung transplantation are surgical treatment options available in a very select group of COPD patients.

Current drug therapy for COPD in Canada:

Inhaled drug treatments for COPD: Short acting beta agonists (SABA), short acting muscarinic antagonists (SAMA), long acting beta agonists (LABA), long acting muscarinic antagonists (LAMA), inhaled corticosteroids (ICS)

Oral drug treatments for COPD: Macrolide maintenance therapy, Roflumilast, N-Acetylcysteine.

Oral opioids are used in selected patients with advanced dyspnea.

The current 2023 Canadian Thoracic Society Guideline on Pharmacotherapy in Patients with Stable COPD recommends:

1) **To reduce symptom burden and improve health status:**

In individuals with stable COPD, at low risk of exacerbations, with low symptom burden and health status impairment (CAT <10, mMRC 1), and only mildly impaired lung function (FEV1≥80% predicted), we recommend starting initial monotherapy with either LAMA or LABA.

In individuals with stable COPD, at low risk of exacerbations, with a moderate to high symptom burden/health status impairment (CAT ≥10, mMRC ≥2) and impaired lung function (FEV1 < 80% predicted), we recommend starting LAMA/LABA dual therapy as initial maintenance therapy.

In individuals with stable COPD, at low risk of exacerbations, with a moderate to high symptom burden and/or health status impairment (CAT ≥10, mMRC ≥2) and impaired lung function (FEV1 < 80% predicted) despite LAMA/LABA dual therapy or ICS/LABA combination therapy, we recommend step-up to a LAMA/LABA/ICS triple combination therapy.

In individuals with stable COPD, at low risk of exacerbations§, with a moderate to high symptom burden and/or health status impairment (CAT ≥10, mMRC ≥2) and impaired lung function (FEV1 < 80% predicted) despite LAMA/LABA/ICS triple combination therapy, we suggest not stepping down to LAMA/LABA dual therapy. For patients taking LAMA/LABA dual therapy, we suggest not stepping down to LAMA or LABA monotherapy

In individuals with stable COPD, at low risk of exacerbations, currently on LAMA monotherapy, LABA monotherapy or LAMA/LABA dual therapy, we do not suggest adding any of the following oral medications: - Phosphodiesterase-4-inhibitors - Mucolytics - Statins - Anabolic steroids - Oral Chinese herbal medicines - Theophylline

In all individuals with stable COPD and at a low risk of exacerbations, we recommend against treatment with ICS monotherapy.

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2) To reduce the risk of acute exacerbations:

In individuals with stable COPD, at low risk of exacerbations, a moderate to high symptom burden and/or health status impairment (CAT ≥10, mMRC ≥2) and impaired lung function (FEV1 < 80% predicted), we recommend starting LAMA/LABA dual therapy as initial maintenance therapy.

In individuals with stable COPD, at high risk of exacerbations*, with a moderate to high symptom burden and/or health status impairment (CAT ≥10, mMRC ≥2) and impaired lung function (FEV1 < 80% predicted), we recommend the use of LAMA/LABA/ICS triple combination therapy.

In individuals with stable COPD, at a high risk of exacerbations*, with a moderate to high symptom burden and/or health status impairment (CAT ≥10, mMRC ≥2) and impaired lung function (FEV1<80% predicted), we do not suggest step down from LAMA/LABA/ICS triple combination therapy to LAMA/LABA dual therapy.

In individuals with stable COPD, at a high risk of exacerbations*, with a moderate to high symptom burden and/or health status impairment (CAT ≥10, mMRC ≥2) and impaired lung function (FEV1 < 80% predicted) who continue to exacerbate (either moderate or severe) despite being on LAMA/ LABA/ICS triple combination therapy, we recommend the addition of macrolide maintenance therapy

In individuals with stable COPD, with a Chronic Bronchitis Phenotype at a high risk of exacerbations*, with a moderate to high symptom burden and/ or health status impairment (CAT ≥10, mMRC ≥2) and impaired lung function (FEV1 < 80% predicted) who continue to exacerbate despite being on LAMA/LABA/ICS triple combination therapy, we suggest the addition of either Roflumilast or N-Acetylcysteine.

3) To reduce mortality:

In individuals with stable COPD, at a high risk of exacerbations*, with a moderate to high symptom burden and/or health status impairment (CAT ≥10, mMRC ≥2) and impaired lung function (FEV1 <80% predicted), we recommend the use of LAMA/ LABA/ICS triple combination therapy over LABA/LAMA dual therapy.

In individuals with stable COPD, at a high risk of exacerbations*, with a moderate to high symptom burden/health status impairment (CAT ≥10, mMRC ≥2) and impaired lung function (FEV1 <80% predicted) we recommend the use of LAMA/LABA/ICS triple combination therapy over ICS/LABA combination therapy.

Below is the treatment algorithm recommended in the Canadian Thoracic Society Guideline on Pharmacotherapy in Patients with Stable COPD:

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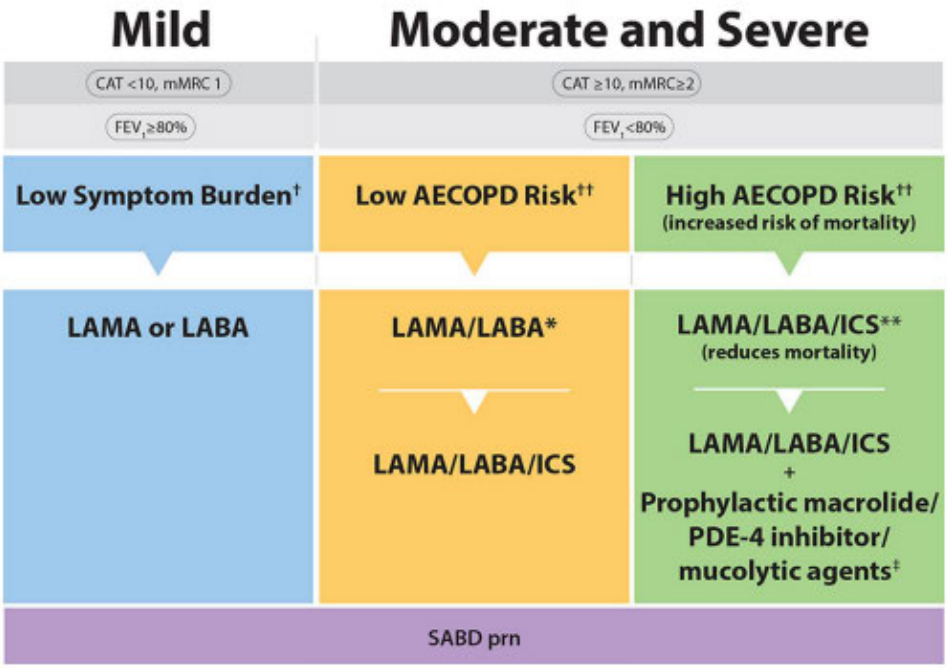

Figure 3. **COPD Pharmacotherapy**.
This figure promotes an evidence-informed approach that aligns proven effective treatments with spirometry, symptom burden, risk of future exacerbations and mortality risk. Because of the clinical heterogeneity in COPD, spirometry should not be used in isolation to assess disease severity and this is why it is also important to perform a thorough clinical evaluation of the patient, including symptom burden and risk of exacerbations that permits the implementation of treatments that are specific for subpopulations. SABD prn (as needed) should accompany all recommended therapies across the spectrum of COPD.
†Symptom burden encompasses shortness of breath, activity limitation, and impaired health status.
††Individuals are considered at "Low Risk of AECOPD" if ≤1 moderate AECOPD in the last year (moderate AECOPD is an event with prescribed antibiotic and/or oral corticosteroids) *and* did not require hospital admission/ED visit. Individuals are considered at "High Risk of AECOPD" if ≥2 moderate AECOPD *or* ≥1 severe exacerbation in the last year (severe AECOPD is an event requiring hospitalization or ED visit).
*LAMA/LABA single inhaled dual therapy is preferred over ICS/LABA inhaled combination therapy considering the additional improvements in lung function and the lower rates of adverse events such as pneumonia. ICS/LABA combination therapy should be used in individuals with concomitant asthma. There is no universally accepted definition of concomitant asthma. The 2017 CTS Position Statement on COPD Pharmacotherapy provides guidance on the assessment of patients who may have concomitant asthma.
**Triple inhaled ICS/LAMA/LABA combination therapy should preferably be administered in a single inhaler triple therapy (SITT), and not in multiple inhalers (see text), although we acknowledge that some patients continue to prefer separate inhalers. ‡Oral pharmacotherapies in this group include prophylactic macrolide, and PDE-4 inhibitor and mucolytic agents for patients with chronic bronchitis.
Abbreviations. CAT, COPD assessment test; mMRC, Modified Medical Research Council; SABD prn, short-acting bronchodilator as needed; AECOPD, acute exacerbation of COPD; ED, emergency department; LAMA, long-acting muscarinic antagonist; LABA, long-acting β2-agonist; ICS, inhaled corticosteroid.

References:

1) Venkatesan, P. (2024). GOLD COPD report: 2024 update. *The Lancet Respiratory Medicine*, *12*(1), 15-16.

2) Bourbeau, J., Bhutani, M., Hernandez, P., Aaron, S. D., Beauchesne, M. F., Kermelly, S. B., ... & Marciniuk, D. D. (2023). 2023 Canadian Thoracic Society guideline on pharmacotherapy in patients with stable COPD. *Chest*.

3) Marciniuk, D., Goodridge, D.,Hernandez, P.,Rocker, G.,Balter, M., Bailey, P., …& Brown C. (2011) Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: A Canadian Thoracic Society clinical practice guideline. Can Respir J.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Despite advances in and increased implementation of pharmacotherapy and nonpharmacologic therapies, COPD remains the 3rd leading cause of death globally and the leading cause of hospital admission and readmission in Canada. A common reason for patients living with COPD to be admitted to hospital is due to COPD exacerbations (aka AECOPD), which can be triggered by many factors including bacteria and viruses, environmental exposures such as pollution or wildfires, comorbid conditions and/or progression of their disease. It is well established that the greatest predictor of future exacerbation is having had a prior exacerbation. The consequences of exacerbations are many and include accelerated loss of lung function, loss of physical function and frailty, worse quality of life, social isolation, increased risk of cardiovascular events and death. The adverse impact on these patients' lives is not to be underestimated. Preventing exacerbations is one of the essential treatment goals for both clinicians and patients living with COPD.

Importantly, even with implementation of the current best evidence guidelines, there is still a significant proportion of patients who continue to have acute exacerbations of their COPD and ongoing symptoms that impact their function. Depending on the study, the prevalence of 'frequent' exacerbations as defined as 2 or more courses of prednisone +/- antibiotics in a year ranges from 17% to 34%. In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study of COPD exacerbation susceptibility, approximately 20% of patients with Global initiative for chronic Obstructive Lung Disease (GOLD) stage 2 disease and as many as 47% of those with stage 4 disease were classified as "frequent exacerbators" (defined as two or more exacerbations annually)[1]. For patients with COPD at high risk of exacerbations triple therapy with LAMA/LABA/ICS reduces the risk of moderate to severe exacerbations but, even with triple therapy, the risk of exacerbations remains high with an average of between 0.91-1.08 moderate to severe exacerbations per year [2,3]. Unlike exacerbations of asthma, exacerbations of COPD can be more severe, require hospitalization and often lead to the prolonged length of stay in hospital, can be associated with respiratory failure requiring invasive or non-invasive ventilation, and may lead to the need for physical rehabilitation. Exacerbations can also be associated with other medical problems like deep venous thrombosis, pulmonary emboli, heart failure, arrhythmias, kidney failure and pneumonia. As such, preventing exacerbations of COPD is a high priority.

A serious issue related to patients with COPD who have exacerbations is that they are often treated with recurring courses of oral prednisone +/- antibiotics, which have significant side effects. It is well established that even small amounts of oral prednisone (e.g. 1 gram per year) can lead to long term consequences such as increased risk of osteoporosis and bone fractures, diabetes, infections, cataracts and glaucoma [4].

COPD is a heterogeneous disease, and it has become clear that different factors interact within individuals with COPD and impact their prognosis. An individual's phenotype is the observable characteristics of an individual that result from their genetic make-up and interaction with their environment. Being able to phenotype a patient with COPD allows a clinician to potentially personalize the treatment approach for individual patients to optimize their outcomes.

COPD is well known to be associated with inflammation in the airways. It was previously thought that most patients with COPD express what is referred to as Type 1 and 3 inflammation, involving inflammatory cells such as macrophages and neutrophils in their disease, as well as proinflammatory mediators (e.g. TNF, IL-6). However, recent evidence suggests that up to 30% of patients with COPD express Type 2 (T2) inflammation [5]. Type 2 (T2) inflammation is characterized by the presence of Th2 cells, which secrete several inflammatory cytokines, namely IL-4, IL-5, and IL-13. IL-4 and IL-13 play an important role in causing allergic and eosinophilic inflammation, and mucus hyper-secretion from the lining of airways. IL-4 also stimulate B cell proliferation, as well as activation of eosinophils, basophils and mast cells. IL-5 is also an important signaling messenger that is responsible for the recruitment, activation and survival of eosinophils in the immune system response. Although there are multiple pathways involved in the T2 inflammatory response, measurement of blood eosinophil count (BEC) in the blood is the most common method used to identify this type of inflammation. The presence of eosinophils (measured in the blood) was historically a differentiating feature of asthma from COPD. However, high eosinophilic count in the blood is now understood to play a role in guiding therapy for COPD, as high blood eosinophil count (BEC) can be a biomarker for predicting response to therapy [6] and has also been associated with increased frequency of

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exacerbations [7,8]. Therefore, there has been a shift in our treatment paradigm to target the suppression of eosinophils with inhaled or oral steroids, however, in many cases, exacerbations persist despite optimum therapy.

References:

1) Hurst et al. N Engl J Med 2010;363:1128-38.

2) Klaus, R. et al. N Engl J Med 2022;383:35-48

3) Lipson, DA,. et al. N Engl J Med 2018;378:1671-1680
4) David Price et al. European Respiratory Review 2020 29(155): 190151; DOI: https://doi.org/10.1183/16000617.0151-2019 2020
5) Chen et al. International Journal of Chronic Obstructive Pulmonary Disease 2022:17 2187–2200
6) Bafadhel, M., Peterson, S., De Blas, M.A., Calverley, P.M., Rennard, S.I., Richter, K. and Fagerås, M., 2018. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. The Lancet Respiratory Medicine, 6(2), pp.117-126.

7) Bafadhel M, McKenna S, Terry S, Mistry V, Reid C, Haldar P, McCormick M, Haldar K, Kebadze T, Duvoix A, Lindblad K. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. American journal of respiratory and critical care medicine. 2011 Sep 15;184(6):662-71.
8) Pascoe S, Barnes N, Brusselle G, Compton C, Criner GJ, Dransfield MT, Halpin DM, Han MK, Hartley B, Lange P, Lettis S. Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: analysis of the IMPACT trial. The Lancet Respiratory Medicine. 2019 Sep 1;7(9):745-56.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Dupilumab targets type II inflammation by blocking the alpha subunit of the interleukin (IL)-4 receptor and inhibiting signaling pathways of IL-4 and IL-13. This mechanism of action is distinct from currently available therapies for COPD patients, which typically include inhaled long-acting beta-agonists (LABA), long-acting muscarinic antagonists (LAMA), and inhaled or oral corticosteroids. In cases of more severe COPD with a high risk of acute exacerbations, prophylactic macrolides, PDE-4 inhibitors, or mucolytic agents may be added to the treatment regimen.

If approved, Dupilumab would be the first biologic therapy available for patients with COPD and would thus represent a paradigm shift by providing a more targeted therapy than has been available to date. No other treatment currently available is targeted to specific inflammatory pathways and the mechanism of action of Dupilumab is complementary to existing treatments as it is the first to specifically inhibit the IL-4/IL-13 pathway. Targeting this pathway has demonstrated a 30-34% reduction in exacerbations on top of ICS/LAMA/LAMA therapy and improvement in FEV1 by approximately 83ml [1,2]. The available totality of evidence suggests dupilumab targets improvement in airway inflammation, reduces mucus lining the airways, and thereby reduces the risk exacerbations and improves quality of life.

Dupilumab would be a valuable addition to the current treatment framework as an add on therapy for patients who remain at high risk of exacerbations despite optimized inhaled triple therapy and have evidence of type 2 inflammation as measured by a blood eosinophil count ≥300. Dupilumab could be considered alongside oral therapies including prophylactic macrolides, PDE-4 inhibitors and mucolytic agents and to be reserved for patients who exhibit a type 2 inflammatory phenotype. Long-term macrolide antibiotic therapy has been associated with risks of antimicrobial resistance, diarrhea, deafness, and heart arrhythmias. Oral PDE-4 inhibitors most commonly cause diarrhea and nausea. Patients would need to be informed about the potential benefits and harms of all therapies in order to make an informed decision of care. The clinical trials assessing efficacy of Dupilumab did not recruit patients who were required to be on triple inhaler therapy plus additional oral therapies; therefore, it would not be our recommendation to require COPD patients to be treated with oral therapies prior to initiation with Dupilumab, provided they meet the other previously stated criteria (high risk of exacerbations despite inhaled triple therapy and evidence of type 2 inflammation).

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References:

1) Bhatt S, et al. N Engl J Med 2023;389:205-214
2) Bhatt S, et al. N Engl J Med 2024;390:2274-2283

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

The patients most likely to respond to treatment are those with type 2 inflammation who are at high risk for COPD exacerbations despite triple inhaled therapy. High exacerbation risk is defined as exacerbation history of ≥2 moderate* or ≥1 severe** within the past year. Those with type 2 inflammation, as defined in the BOREAS and NOTUS clinical trials, had a blood eosinophil count (BEC) >= 300. BEC appears to be most useful in those with high exacerbation risk as evidenced by prior exacerbations.

Exacerbations of COPD remain a significant challenge for patients and the health care system. Underdiagnosis and lack of access to spirometry testing and specialist care remain significant barriers for people with COPD to access appropriate care and reduce the risk of exacerbations of COPD. However, it is well established that there are still patients with COPD who continue to be at high risk of exacerbations despite having a confirmed diagnosis, access to primary or specialty care and being on optimal medical therapy. Of these patients, those with signs of type 2 inflammation are those most in need of this treatment.

Currently, patients with COPD who have exacerbations frequently receive 5-7 days of oral corticosteroids and antibiotics to treat their exacerbation. Use of oral steroids and antibiotics can be associated with both acute and long-term side effects and can lead to a decrease in quality of life. A COPD exacerbation has the same in-hospital mortality and 1-year post-exacerbation mortality profiles as myocardial infarction. In addition to a significant burden associated with the loss of autonomy and productivity, increased anxiety and depression are associated with these events.

The patients best suited for treatment would be identified by a treating respirologist. If identified by a primary care physician, our recommendation would be that they be referred to a respirologist. They should have confirmation of a diagnosis of COPD based on symptoms and spirometry showing fixed obstruction (FEV1/FVC < 0.7 and/or lower limit of normal). Misdiagnosis of COPD does occur, but it is our recommendation that use of this drug be restricted to respirologists who look after COPD and thus the appropriate diagnostic test will be conducted and the chance of any misdiagnoses and thus any misuse of the drug would be very small.

The clinical efficacy of dupilumab in COPD appears to be correlated with a blood eosinophil count greater than 300 cells per microliter. This test is affordable and obtained with a simple blood count that is available in all regions of Canada.

*Moderate exacerbations are defined as an AECOPD that require either systemic corticosteroids (intramuscular (IM), intravenous, or oral) and/or antibiotics.

**Severe exacerbations are defined as an AECOPD requiring hospitalization, emergency room, or urgent care visit.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Biologic therapies like dupilumab should be integrated into COPD treatment with specific goals in mind. These objectives include reducing the frequency and severity of symptoms, improving quality of life (such as better exercise tolerance and increased work attendance), decreasing exacerbations, and minimizing side effects from existing maximal therapies (like those related to steroid use). There is also the potential to reduce the daily medication burden and enhance treatment adherence.

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In clinical trials, dupilumab showed a significant decrease in the annual rate of severe exacerbations. Standard clinical assessments, such as the COPD Assessment Test, along with evaluations of FEV1 and exacerbation rates, are commonly used and consistently applied by specialist physicians.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

When considering the discontinuation of dupilumab treatment, several factors must be evaluated. These include the absence of clinically meaningful improvements within the expected timeframe, such as annual exacerbation rates remaining consistent with pre-treatment levels, significant worsening in pre-bronchodilator FEV1 and patient symptom scores It is important to note that the natural history of lung function (measured by FEV1) is that it will decrease with age in an adult population. Therefore, we expect most patients with COPD to have a gradual decline in lung function over time. On average, a FEV1 decline of approximately 30ml is considered within a normal aging process. Generally, it is recommended that at least 6 months on biologic should be tried before making a decision to discontinue (in the absence of an important side effect necessitating discontinuation). Additionally, safety concerns related to significant systemic adverse events, along with patient preferences like treatment fatigue, can also impact the decision to stop therapy.

Conversely, a positive response in one or more of these areas may justify continuing dupilumab treatment.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

It is recommended that the first one or more doses of dupilumab should be administered by a healthcare professional in a clinical setting to ensure correct technique for administration (e.g., identifying appropriate injection site, depth of injection) and tolerance by the patient. Following this, injection by the patient or a caregiver can be undertaken in the community setting, at home, after the healthcare professional determines it is appropriate and the patient or caregiver has received proper training on correct administration.

A Respirologist is required to diagnose, treat and monitor patients who might receive the drug under review.

6. Additional Information

Consideration should be given to the use of large databases from primary and secondary care to evaluate the longer-term benefits of Dupilumab, including cost effective analyses.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No. We completed this response without any financial or logistical support.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No outside help was provided to us for the information included in this report.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Imran Satia
Position: Associate Professor, Respirologist, McMaster University
Date: 11/12/2024

X **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
GSK			X	
AstraZeneca			X	
Sanofi-Regeneron			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Anthony D'Urzo
Position: Physician Primary Care Lung Clinic
Date: 11/12/2024

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**

GSK			X	
AstraZeneca			X	
Sanofi-Regeneron			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Erika Dianne Penz
Position: Associate Professor, University of Saskatchewan; President-Elect, Canadian Thoracic Society
Date: 09-12-2024

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AstraZeneca				x
GSK			x	
Sanofi		x		
Valeo	x			
COVIS Pharma	x			
Lung Saskatchewan	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: David Gourde
Position: Nurse clinician Certified respiratory Educator Co-Chair of the COPD Clinical assembly of the Canadian thoracic Society
Date: 14-12-2024

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
GSK		X		
Trudell Medical Int	X			
AstraZeneca	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Joshua Wald
Position: Associate professor, McMaster University; Co-chair, Canadian Thoracic Society COPD Assembly
Date: 09-12-2024

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
AstraZeneca		X		
GSK			X	
Sanofi		X		
Roche	X			
The Lung Health Foundation	X			

* Place an X in the appropriate dollar range cells for each company.

CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Dupilumab (Dupixent)

Indication: Add-on maintenance treatment in adult patients with uncontrolled chronic obstructive pulmonary disease (COPD) associated with type 2 inflammation.

Name of Patient Group: Submission by Lung Health Foundation

Author of Submission: Sonia Cardozo, Laura Bifolchi - Lung Health Foundation

1. About Your Patient Group

This patient input submission is submitted by Lung Health Foundation (LHF).

The Lung Health Foundation (www.lunghealth.ca) legally known as the Ontario Lung Association, is registered with the CADTH and pCODR, and stands as a cornerstone of trust and reliability in the Canadian healthcare and public health systems. Lung Health Foundation is a registered charity that assists and empowers people living with or caring for others with lung disease. It is a recognized leader, voice and primary resource in the prevention and control of respiratory illness, tobacco cessation and prevention, and its effects on lung health. We are governed by a dedicated board of directors and supported by a team of approximately 40 employees alongside thousands of passionate volunteers. Together, we work tirelessly to improve the lung health of Canadians, driving positive change and fostering a brighter, healthier future for all.

2. Information Gathering

Data Collection
The information provided by the Lung Health Foundation in this submission builds from our robust experience working directly with people living with chronic obstructive pulmonary disease (COPD). The data was collected through various methods, including an online survey completed by 27 individuals with COPD, feedback from monthly support group sessions, one-on-one virtual appointments with Certified Respiratory Educators (CREs), and a virtual patient interview.

Demographic Data
The online survey was conducted using Alchemer and included responses from 27 participants across Canada between December 2022 and December 2024. However, age and gender data were not collected through this survey tool. The support group feedback was gathered from seven individuals living with COPD in Ontario. These participants provided their insights through a verbal survey.

The one-on-one virtual CRE appointments were conducted via Zoom between March and November 2024. Four individuals participated in these sessions, consisting of two males and two females all of whom reside in Ontario. Each individual met with a CRE eight times for one-hour sessions.

Lastly, two virtual patient interviews were conducted to gather additional insights. The first interview took place in December 2024 with [redacted], a 72-year-old male living with COPD in Nelson, British Columbia. This interview was conducted via telephone. The second interview was held in November 2024 with JS, a 46-year-old male living with severe asthma in New Brunswick. This session was conducted through video conferencing.

Summary of demographic data:

Name	Patient/ Caregiver	Gender	Age	Diagnosis	Diagnosis Date	Location	Source
[redacted]	Patient	M	72	COPD	2004	Nelson, BC	Telephone Interview
[redacted]	Patient	F	72	COPD	2014	Toronto, ON	1:1 CRE appt
[redacted]	Patient	F	65	COPD, Asthma	1995	Pickering, ON	1:1 CRE appt
[redacted]	Patient	M	70	COPD	2000	Hagersville, ON	1:1 CRE appt
[redacted]	Patient	M	50	COPD	2023	Sebright, ON	1:1 CRE appt
Respondent 231	Patient	n/a	64	n/a	n/a	n/a	Online Survey
[redacted]	Patient	F	n/a	n/a	n/a	n/a	Online Survey
[redacted]	Patient	M	46	Severe Asthma	n/a	New Brunswick	Virtual 1:1 Meeting

3. Disease Experience

Our online survey data highlights that the top symptoms experienced by participants include shortness of breath (88.9%), fatigue (74.1%), and coughing (44.4%). These symptoms significantly impact daily life, with participants reporting difficulties with housework (70.4%), sports and physical activities (66.7%), and walking upstairs (59.3%). One respondent, [redacted] shared: "I struggle to enjoy the same activities that I used to because of my shortness of breath. I used to love dancing and now I must take rest breaks frequently and make sure I do not overdo it to preserve my energy".

Similarly, insights from our support group revealed that 100% of participants sought relief from bothersome symptoms, particularly shortness of breath on exertion and coughing. Additionally, 14% ranked frequent exacerbations and side effects from Prednisone as their most significant concerns.

The 1:1 CRE appointments with four patients echoed these findings as well, as all identified shortness of breath on exertion as their most limiting symptom. [redacted] stated: "I no longer leave the house because I am too breathless. Not being able to connect with family and friends like I used to is making me feel very depressed and angry". Another patient, [redacted], shared: "Even working virtually from home is challenging—some days, simply speaking in meetings leaves me short of breath and fatigued."

Living with COPD often results in significant negative life impacts. Survey respondents cited being unable to do daily activities due to shortness of breath (77.8%), fatigue (66.7%), and feelings of isolation (48.1%) as the most common

challenges. [redacted] shared a similar perspective: “I don’t feel like going out anymore. I have to plan every minute of my day, which is exhausting. It’s easier to stay home, and I’ve become a hermit because of it. I feel really isolated at times because I live on my own too.”

These findings emphasize the profound physical, emotional, and social toll of COPD. Symptoms such as shortness of breath and fatigue significantly limit daily activities and contribute to feelings of isolation and frustration. Patients need treatments that not only address physical symptoms but also enhance their ability to engage in meaningful activities and improve their overall quality of life.

4. Experiences With Currently Available Treatments

Survey respondents identified several benefits of current COPD treatments, with the most common being reduced shortness of breath (70.4%), increased ability to exercise (40.7%), improved participation in daily activities (25.9%), and reduced coughing (25.9%). [redacted] reflected these sentiments, noting: “I have more energy since starting triple therapy, and I don’t get tired as easily.”

In the 1:1 CRE appointments, all respondents reported using LAMA, LABA, and ICS therapies, with 75% also using SABA as needed. Among those using SABA, 25% used it 10 times per week, 25% used it 21 times per week, and another 25% used a combination of SABA and SAMA up to 28 times per week. Despite adherence to prescribed medications, all participants reported ongoing challenges with shortness of breath on exertion. [redacted] explained: “I still have to use my SABA before any activity, or I won’t last long without stopping.”

A recurring theme among participants was hesitancy to initiate the yellow zone of their COPD action plans due to concerns over Prednisone’s side effects. In a support group poll, 14% identified Prednisone’s side effects as their primary concern, with others agreeing that this was a significant challenge in managing their condition.
When asked about side effects from current treatments, 44% of online survey respondents reported no side effects. Among those who did, voice hoarseness (33%), difficulty sleeping (26%), and low energy (15%) were the most common.

While current COPD treatments provide meaningful benefits such as reduced shortness of breath and increased ability to exercise, significant challenges remain. Patients continue to face limitations in their daily lives due to residual symptoms and side effects. These findings highlight the urgent need for additional COPD medications that address unmet needs, minimize side effects, enhance overall treatment outcomes, and improve quality of life.

5. Improved Outcomes

Key treatment outcomes identified by COPD patients in our online survey revealed that 77.8% prioritized improved quality of life, 59.3% sought a reduction in symptoms, 44.4% desired increased energy, and 40.7% highlighted better symptom management. Similarly, support group feedback underscored reduction in symptoms (86%), enhanced quality of life (57%), and improved energy (57%) as critical needs.

Patients expressed a clear desire for treatments that allow them to live fuller, less restricted lives. As one participant, [redacted] shared: “I want to make the most of my life and live in the moment without worrying about my medications, my oxygen, or having a flare-up. I’d love to go for a long walk outside like I used to and be able to last longer.”

The need for greater symptom relief and control was echoed by many patients with severe COPD. One **Respondent 231** stated: “I am only 64 years old and have very severe stage 4 COPD. I would appreciate any new medications that could help me function better.” Another patient, [redacted] described the daily challenges of the disease: “Some days I feel

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completely breathless without any activity. I feel like I'm fighting my lungs to work the way I want them to, but they resist. It's a constant battle not to feel depressed—I feel like I'm being robbed of my life."

These insights highlight the urgent need for new medications that go beyond symptom management to significantly improve the quality of life for those living with COPD.

6. Experience With Drug Under Review

There were no patients in this submission group that had experience on Dupilumab for add-on maintenance treatment with uncontrolled chronic obstructive pulmonary disease (COPD) associated with type 2 inflammation. However, we were able to interview [redacted] who had been using Dupilumab for severe asthma. As part of his treatment plan for severe asthma, [redacted] was frequently prescribed steroids. This course of treatment contributed to weight gain which made him less active and made his asthma worse. Since using Dupilumab he has lost weight and become more active, and his severe asthma is better managed.

7. Companion Diagnostic Test

N/A

8. Anything Else?

There is an unmet need for COPD therapies that will improve health-related quality of life for patients. Our patients consistently raise their quality of life as a critical consideration when balancing benefits and risks when they are working with their physicians to select their treatment options. Lung Health Foundation strongly urges the Canada Drug Agency to recognize the gap and barrier to adequate treatment options that are specific to these patients. They deserve treatments that will work, that are affordable, and that are accessible across Canada.

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Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.
   No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.
   No

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range with an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Sanofi-Regeneron			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Riley Sanders
Position: Senior Manager, Public Affairs
Patient Group: Lung Health Foundation (Legal name: Ontario Lung Association)
Date: December 19th, 2024

CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Dupilumab (Dupixent)
Indication: Chronic Obstructive Pulmonary Disease (COPD)
Name of Patient Group: Chronic Obstructive Pulmonary Disease Association (COPD Canada)
Author of Submission: Henry Roberts

1. About Your Patient Group

Chronic Obstructive Pulmonary Disease Association (COPD Canada) is a non-profit patient advocacy association that was established in 2005 and operates independently. The association's primary mandate is to inform and support Canadians who live with the challenges of chronic obstructive pulmonary disease (COPD).

At the core of COPD Canada lies our commitment to building, advocating for, and maintaining a national community of patients burdened with COPD. We strive to enhance public awareness and visibility of this condition throughout the nation. To achieve this, we offer various educational and related medical information delivered to our membership and the larger Canadian COPD population using different formats and employing diverse delivery methods - through our website, via social media, print, TV and radio. The association also advocates for an expanded use of diagnostic testing for all Canadians who currently smoke or have smoked.

With a focus on emphysema and chronic bronchitis COPD Canada reviews and interprets the latest scientific and medical advances from worldwide sources. This information is then made available in easy-to-understand language to our members through our website, social media, and our community newsletter "Living with COPD". All published information is archived and available through the COPD Canada website: https://www.copdcanada.info

Membership to COPD Canada is free-of-charge but is restricted to COPD patients and their caregivers. Individuals can join through the Membership portal on our website and will begin to receive complimentary printed copies of our newsletter. Members are encouraged to add their pulmonary rehab clinic to our mailing list to receive bulk copies of the newsletter, also free-of-charge, for distribution to attending patients.

2. Information Gathering

For the purposes of illustrating the condition-related symptoms and problems that impact a COPD patients' day-to-day activities and quality of life, we are relying primarily on the personal experiences of our members and published scientific papers related to the disease. The experiences that are described are common to most of our members and much of the Canadian population who suffer from chronic obstructive pulmonary disease. Additionally, we have extensive interactions with many non-

member COPD patients. These interactions and conversations occur in group pulmonary rehabilitation settings, lung issue support groups, as well as in direct one-on-one discussions. The common experience of COPD sufferers will be reflected in much of the information presented in this submission.

In November 2024, COPD Canada sent an e-mail survey to our national membership database and received completed survey responses from sixty one members. None of the respondents has had experience with this particular drug although many have had experience with the current triple therapies available – Trelegy and Breztri, or combinations of LAMA + ICS/LABA drugs commonly prescribed in Canada. Seventy-three percent of our respondents have experienced an exacerbation (flare-up) and of those most have experienced a flare-up at least once per year. Forty-nine percent have been hospitalised as a result of an exacerbation.

Demographics: Of the 61 respondents to our survey, 64% were 66-80 years old, 21% were over the age of 80, 15% were aged 50-65

The survey explicitly stated that Dupilumab (Dupixent), manufactured by Sanofi, was the biologic drug that was under review by Canada's Drug Agency (formerly CADTH). We have used relevant quotes from our members and have included those, as appropriate.

"I cannot even take my garbage out, can't walk more than 100 feet without having to stop to catch my breath. I cannot breathe well enough to complete most of my daily chores."

3. Disease Experience

With worsening disease, a COPD patient will progressively become less physically active and will have reduced social contacts. COPD is associated with a considerable burden of disease, affecting many things that are fundamental to everyday life, such as the ability to breathe, talk, sleep, work, and socialize. COPD also has significant extra-pulmonary effects that may contribute to its severity in individual patients and is often accompanied by co-morbidities such as cardiovascular disease.

It has been observed that reduced physical activity in patients with COPD is associated not only with the clinical stages of COPD severity but also with systemic inflammation. Patients with COPD have limitations in their occupational activities as well as in household and leisure time activities. Many patients with COPD are of working age, so even in the early stages of the disease, the breathlessness and fatigue caused by COPD reduces the ability of the patient to go to work or carry out their normal work activities.

Studies have demonstrated that exacerbations are associated with short and long-term consequences on health status. The downward spiral of more frequent exacerbations leads to decline in lung function; greater anxiety; worsening quality of life; social withdrawal; more exacerbations; and increased risk of hospitalization and mortality.[1]

As symptoms worsen, one is usually forced to take early retirement. COPD has an increasingly profound effect on all aspects of one's life, severely impeding the ability to do even the most basic daily tasks, limiting social interactions and causing depression. In addition to the social stigma and isolation that COPD causes, the disease forces one to adapt their lifestyles dramatically. A typical week for a COPD patient consists of reading, spending most of their time indoors, with infrequent outings to attend pulmonary rehabilitation classes.

"I have difficulty doing everyday chores, cannot walk farther than 4 blocks without a rest, interrupts my sleep and scares me badly when an exacerbation causes my throat to spasm and close. I have become isolated and dependent."

Many of the day-to-day activities most take for granted are virtually impossible or extremely difficult for people with severe COPD. These activities include:

- Changing bed sheets
- Bathing and dressing
- Shopping and carrying bags/groceries
- Climbing stairs
- Walking and talking at the same time

While being forced to adapt one's lifestyle in many ways:

- Avoiding restaurants that have stairs or washrooms that are not located on the ground floor.
- Using supplemental oxygen when walking, on aircraft or during pulmonary rehab
- Being extra vigilant of weather conditions to assess wind conditions, humidity and temperature before venturing outside
- Avoiding any exertion outdoors particularly during cold weather or hot humid weather
- Walking at a very slow pace

"Must deal with anxiety associated with having COPD (fearing episodes of shortness of breath), unable to walk very far (or manage hills or inclines), must do all things slowly, cannot lift even slightly heavy items (i.e. bag of groceries)"

4. Experiences With Currently Available Treatments

There is no cure for COPD, and there are no medications that reverse the loss of lung function caused by COPD. No drug has demonstrated effectiveness in halting the progression of the disease. Currently the goal of medications for COPD is to maintain control of symptoms and prevent or minimize the frequency and duration of exacerbations (which can also be referred to as flare-ups or lung attacks).

As the disease progresses, medications are typically added on. Existing COPD management includes medicines to open the airways and reduce inflammation. The main non-medicinal interventions include pulmonary rehabilitation, exercises including breathing lessons and the use of supplemental oxygen.

Surgical options include lung transplantation or lung reduction surgery, which areprdnis extremely invasive procedures that are only available to a small group of COPD patients who qualify as candidates.

Typical maintenance therapy usually includes the use of Spiriva once per day with Advair or Symbicort twice per day. The new triple therapies Trelegy and Breztri are now more widely available, and patients are stepped-up to triple therapy more quickly than previously prescribed. Rescue medications vary from patient to patient although Ventolin is used quite extensively. These medicines are to control the patient's day-to-day condition and symptoms, but they do not improve long-term lung function. When one experiences an exacerbation prednisone and antibiotics are often prescribed. Prednisone works quickly but has very dangerous side effects. The over-use of antibiotics has become a national and international concern due to increased resistance, particularly in long-term care facilities.[2]

"I don't think the medicine I'm taking is controlling my shortness of breath or flare-ups particularly well. Others with COPD have been taking the same Rx for years and seem to be living a normal life. That's never been the case with me no matter what Rx I am taking."

5. Improved Outcomes

COPD patients need additional therapies that work to improve breathing and lung function, are easy to use, and do not just offer symptomatic or emergency relief. Because chronic obstructive pulmonary disease is treated in a stepwise manner, where treatments are layered on as the disease progresses, additional treatment options are often needed to address continual disease progression, particularly as the disease progresses in severity. As well, long term use of some of these compounds results in a diminishing of the drug's effectiveness. Therefore, availability to alternative drugs that can enhance disease management should be encouraged and supported.

Our association is cognizant of access issues throughout Canada, particularly for economically disadvantaged patients and those reliant on the provincial drug plans. The reimbursement of approved medicines for the treatment of COPD varies by province. In Alberta, there is generally favourable access to treatments for patients reliant on the provincial drug plan. However, in Atlantic Canada there is generally poor drug coverage while in Ontario there is moderate drug coverage by the provincial drug plan for approved medications.

Most of our members are over 65 years of age and for many it is a financial imperative that COPD medications be covered by provincial drug plans. Dupixent, with its demonstrated anti-inflammatory properties, would be a welcome addition to provincial formularies across the country.

"I need to increase my oxygen setting once I stand up or start to walk. My oxygen drops too low when I climb stairs, make bed, walk fast, carry anything over 1lb, bend over for at least an hour after eating anything. I do not go into public buildings because with a mask on I quickly become short of breath even though I have my oxygen on."

6. Experience With Drug Under Review

None of our members who responded to the survey has had experience with Dupixent. We asked our members what COPD medications they were taking when they had their last flare-up (exacerbation). Of the forty three respondents to this question, nineteen were taking triple therapy medications: either as a single inhaler (Trelegy or Breztri) or as a combination LAMA + ICS/LABA (Spiriva + Symbicort) when they experienced their last exacerbation.

7. Companion Diagnostic Test

Dupilumab is intended for use in treating chronic obstructive pulmonary disease for patients with high levels of type 2 inflammation which is linked to high levels of eosinophils in the blood. If the patient has elevated eosinophil counts (>300 cells/μL) this can predict or help guide the use of dupilumab which targets this eosinophilic inflammation. Measuring blood eosinophil counts is straightforward and involves the following steps:

1. Blood Draw: A healthcare provider draws a small sample of blood from a vein, typically in the arm.
2. Laboratory Analysis: The blood sample is sent to a lab where automated machines (or sometimes manual microscopy) count the eosinophils, usually as part of a complete blood count (CBC) with a differential. The differential specifies the percentage and absolute number of eosinophils in the blood.

The process of measuring blood eosinophil counts is minimally invasive and not significantly inconvenient. In most Canadian jurisdictions there is not a cost to the patient for this diagnostic test. The time to receive test results vary and typically the results are sent directly to the attending doctor for review with the patient.

8. Anything Else?

Caregivers of COPD patients are impacted to a significant extent and are frequently the spouse or child of the patient. The disease causes serious age-related difficulties, and this is especially true with COPD which is more prevalent and pronounced in older Canadians.

While each caregiver certainly has their own unique experiences and challenges, family caregivers frequently encounter the following burdens:

- limited time for managing their own health and wellbeing
- feelings of depression and isolation
- anxiety, stress, fatigue, unending days
- increased requirements for social support
- in the case of grown children who become their parent's caregivers, they are often torn between the needs of their young families and the needs of their elderly parent with COPD.

"My wife increasingly has to assume responsibility for tasks I can no longer perform"

Despite the availability of national and international guidelines, and effective, well-tolerated pharmacological treatments, COPD remains substantially under-diagnosed and under-treated within primary care.[3] Increasing evidence suggests that initiation of anti-inflammatory agents and long-acting bronchodilators at an early stage can significantly improve the patient's long-term health and quality of life. Recent large-scale trials in COPD have confirmed the long-term benefits of the early initiation of maintenance treatments.

Although there are medications for COPD, patients still complain of symptoms. This brings forth the need for alternative bronchodilators and anti-inflammatory agents that can improve lung function, quality of life, reduce exacerbations and delay disease progression. And, over the long term, improve survival.[4]

"I think I would benefit from an exercise programme or physio. Reduction of exacerbations and shortness of breath. And, if possible, regain (at least some of) my ability to enjoy doing things in life that I was once able to do."

It seems apparent to us that any new COPD therapy, like Dupixent, that is intended to reduce the frequency and duration of exacerbations would be of benefit to the patient as well as the health care system overall. The benefits to society and the healthcare system of this therapy accrue through fewer exacerbations resulting in less use of emergency department services while improving a patient's quality of life. The costs associated with COPD affect the family, the healthcare system, and the community as a whole with loss of productivity and the need for additional healthcare services.[5]

As a national patient advocacy group, we encourage and support additional therapeutic choices in managing this debilitating condition.

1 Activities of Life - The COPD Patient
Journal of COPD, 6:192-200 ISSN: 1541-2555 print / 1541-2563 online

2 Prevalence of multidrug-resistant gram-negative bacteria among nursing home residents: A systematic review and meta-analysis Sainfer Aliyu, Arlene Smaldone, Elaine Larson
American Journal of Infection Control, Vol. 45, Issue 5, p512–518 Published in issue: May 01, 2017

3 Epidemiology and burden of COPD – CTS position statement Pharmacology in patients with COPD
Canadian Journal of Respiratory, Critical Care, and Sleep Medicine – 2017, VOL 1, NO. 4, 222-241

4 Optimising pharmacological maintenance treatment for COPD in primary care
Prim Care Respir J 2011; 21(1): 33-45

5 Public Health Agency of Canada. Centre for Chronic Disease Prevention and Control Chronic Respiratory Diseases. COPD. http://www.phac-aspc.gc.ca/ccdpc-cpcmc/crd-mrc/copd_e.htm

Appendix: Patient Group Conflict of Interest Declaration

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Did you receive help from outside your patient group to collect or analyze data used in this submission? **No**

1. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check the appropriate dollar range with an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Sanofi Canada			X	
AstraZeneca Canada			X	
GSK Canada			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Henry Roberts
Position: Member – Executive Committee
Patient Group: Chronic Obstructive Pulmonary Disease Association (COPD Canada)
Date: December 5, 2024

CADTH Reimbursement Review
Drug Program Input on Implementation Issues

Section 1: General Information

1.1 Drug Product Information:	
Drug name (generic): Dupixent (dupilumab)	**Sponsor:** Sanofi-aventis Canada Inc.
Indication: Under review (pre-NOC) Proposed: Add-on maintenance treatment in adult patients with uncontrolled chronic obstructive pulmonary disease (COPD) associated with type 2 inflammation, if the following conditions are met: - Post-BD FEV1/FVC ratio <0.70 and post-BD FEV1 % predicted >30% and ≤70%, and - Background therapy of ICS+LABA+LAMA or LABA+LAMA if ICS is contraindicated, and - Blood eosinophils ≥300 cells/μL, and ≥2 moderate or ≥1 severe exacerbation* within the past year, and - mMRC≥2 *Moderate exacerbations defined as AECOPD that require either systemic corticosteroids (intramuscular, intravenous, or oral) and/or antibiotics. Severe exacerbations are defined as AECOPD requiring hospitalization or observation >24 hours in emergency department/urgent care facility.	
Reimbursement Request: As an add-on maintenance treatment in adult patients with uncontrolled chronic obstructive pulmonary disease associated with type 2 inflammation, if the following conditions are met: - Post-BD FEV1/FVC ratio <0.70 and post-BD FEV1 % predicted >30% and ≤70%, and - Background therapy of ICS+LABA+LAMA or LABA+LAMA if ICS is contraindicated, and - Blood eosinophils ≥300 cells/μL, and ≥2 moderate or ≥1 severe exacerbation* within the past year, and - mMRC≥2 *Moderate exacerbations defined as AECOPD that require either systemic corticosteroids (intramuscular, intravenous, or oral) and/or antibiotics. Severe exacerbations are defined as AECOPD requiring hospitalization or observation >24 hours in emergency department/urgent care facility.	

1.2 Lead Jurisdiction
Jurisdiction: VAC

A subset of up to 40% of patients with COPD have evidence of type 2 inflammation which is associated with higher mortality, increased risk of exacerbations, lower FEV1, higher impairment in health status, higher health care utilization and increased risk of mortality.

Treatment recommendations from the Canadian Thoracic Society (CTS) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) state patients with moderate and severe disease and a high risk of COPD exacerbation (≥2 moderate exacerbations or ≥1 severe exacerbation; aligned with GOLD group E) should be treated with long-acting muscarinic antagonists (LAMA)+ long-acting beta agonist (LABA)+ inhaled corticosteroids (ICS) administered as a single inhaled triple therapy or LAMA+LABA if there is a contraindication to ICS. The recent 2025 update to the GOLD guidelines recommend dupilumab for patients with eosinophils ≥300cells/μL, who have been treated with LABA+LAMA+ICS and continue to experience exacerbations and have symptoms of chronic bronchitis.

Section 2: Jurisdictional Implementation Issues

Table 1: Jurisdictional Context

2.1 RELEVANT COMPARATORS Check (type "X") whether you have identified potential or current **issues** and provide brief details	
☐X	**a) Issues with the choice of comparator in the submitted trial(s)** The efficacy and safety of dupilumab was assessed in two multinational, randomized, double-blind, placebo-controlled, phase 3 trials (BOREAS and NOTUS). Both trials were designed and conducted to investigate the efficacy and safety of dupilumab 300mg SC q2w over 52 weeks in patients with uncontrolled COPD (i.e., ≥2 moderate or ≥ 1 severe exacerbations in the previous year and mMRC ≥2) and moderate-to-severe airflow obstruction (i.e., post-BD FEV1 >30% to ≤70% of predicted) despite receiving maximum best supportive care (BSC) background therapy, including LABA, LAMA, and ICS (unless ICS was contraindicated). The primary endpoint of both trials was annualized rate of acute moderate or severe COPD exacerbation (AECOPD) over the 52-week treatment period compared to placebo. In both studies, dupilumab 300 mg q2w led to a significant and clinically relevant reduction in the annualized rate of moderate or severe AECOPD during the 52-week intervention period (30% reduction in BOREAS and 34% reduction in NOTUS compared with placebo). The key secondary endpoints were pre-BD FEV1 over 12 weeks compared to placebo; health related quality of life, assessed by the change from baseline to Week 52 in the St. George's Respiratory Questionnaire (SGRQ) and evaluating respiratory symptoms (E-RS); and pre-BD FEV1 over 52 weeks compared to placebo. Both trials were placebo controlled. Did not compare dupilumab add-on therapy to add-on therapy with azithromycin, roflumilast or N-acetylcysteine. NOTE: Canadian clinical experts indicated that roflumilast and azithromycin are rarely used in the maintenance treatment of COPD (adverse events, safety concerns, microbial resistance)
☐X	**b) Other implementation issues regarding relevant comparators (e.g., access/funding, covered population)** Roflumilast is not covered by any jurisdictions in Canada, however as noted above roflumilast is rarely used and may not be considered a relevant comparator.

Table 2: Policy Considerations for Reimbursing the Drug

2.2 CONSIDERATIONS FOR INITIATION OF THERAPY Check any category where you have identified potential or current **issues** and provide brief details	
☐X	**a) Disease diagnosis, scoring or staging for eligibility** Inclusion criteria for trials: - A diagnosis of moderate to severe COPD (postbronchodilator spirometry FEV1/FVC ratio < 0.7 and post-bronchodilator FEV1% predicted >30% to ≤70%. - Current or former smokers with a smoking history of at least 10 pack years. - Medical Research Council (MRC) Dyspnea scale grade ≥2 - Patient-reported history of signs and symptoms of chronic bronchitis (chronic productive cough) for 3 months in the year up to screening in the absence of other known causes of chronic cough

	- Documented history of high exacerbation risk defined as exacerbation history of ≥2 moderate* or ≥1 severe** within the year prior to inclusion. At least one exacerbation should have occurred while the patient was taking ICS/LAMA/LABA (or LAMA/LABA if ICS is contradicted) *Moderate exacerbations were recorded by the Investigator and defined as AECOPD that require either systemic corticosteroids (intramuscular, intravenous, or oral) and/or antibiotics. One of the 2 required moderate exacerbations had to require the use of systemic corticosteroids. **Severe exacerbations were recorded by the Investigator and defined as AECOPD requiring hospitalization or observation >24 hours in emergency department/urgent care facility. - Background triple therapy (ICS + LABA + LAMA) for 3 months prior to randomization with a stable dose of medication for ≥1 month prior to Visit 1: (Double therapy: LABA + LAMA allowed if ICS was contraindicated). - Evidence of type 2 inflammation: Patients with blood eosinophils ≥300 cells/microliter at Visit 1 (Screening). Question for the clinical expert: Should all inclusion criteria used in the trials be required to be eligible for treatment with dupilumab? Are there any other parameters that should be considered to determine eligibility for treatment with dupilumab?
☐X	**b) Other patient characteristics for eligibility (e.g., age restrictions, comorbidities)** Question for the expert: Would dupilumab be considered in patients who fall outside the target populations of the clinical trials (e.g., those who have a history of or a current diagnosis of asthma, outside age range used in trials, etc.)?
☐ X	**c) Prior therapies required for eligibility** As per the indication, the patient should be currently using triple therapy (ICS+LAMA+LABA) or dual therapy (LAMA+LABA) if ICS is contraindicated. Question for the clinical expert: What should be the duration of triple (or dual) therapy use that would be required prior to add-on therapy with dupilumab?
☐	**d) Eligibility to re-treatment** Example: Can the drug be given again to patients who relapsed while off therapy? If so, what would be the appropriate timing of re-treatment?
☐	**e) Special subtypes (not explicitly mentioned in the indication) to consider separately for eligibility** Example: Would patients with CNS metastases equally benefit from this oncology drug and would they be considered eligible?
☐	**f) Consistency with initiation criteria associated with other drugs reviewed by CADTH in the same therapeutic space** Example: Consider alignment with reimbursement criteria for drug B.
2.3 CONSIDERATIONS FOR CONTINUATION OR RENEWAL OF THERAPY Check any category where you have identified potential or current **issues** and provide brief details	
☐X	**a) Challenges related to assessment and monitoring of therapeutic response** Onset of the dupilumab treatment effects as add-on treatment to current BSC was apparent within 2 weeks of initiation of dupilumab treatment and was maintained at Week 52. A return to baseline COPD, including increased exacerbations, decreased pre-BD FEV1, and increased SGRQ, was noted after dupilumab treatment discontinuation, supporting the need for long-term dupilumab therapy.

	In addition to the primary benefit in reducing the frequency of moderate or severe exacerbations, dupilumab also led to a statistically significant and clinically relevant improvement in the participants' lung function, as demonstrated by statistically significant improvements in pre-BD FEV1 at Week 12 and Week 52 as compared to placebo. It also improved health status/HRQoL Question for the clinical expert: After starting dupilumab, when should follow-up occur to determine therapeutic response (i.e., 12 weeks)? What parameters would be used to determine therapeutic response?
☐	**b) Consistency with renewal criteria associated with other drugs reviewed by CADTH in the same therapeutic space** Example: Consider alignment with renewal criteria for drug B.
2.4 CONSIDERATIONS FOR DISCONTINUATION OF THERAPY Check any category where you have identified potential or current **issues** and provide brief details	
☐X	**a) Definition of loss of response, absence of clinical benefit, or disease progression** In the trials, consistent benefit was seen across subgroups of baseline biomarkers (including biomarkers of type 2 inflammation), with a trend towards numerically greater improvements with increased type 2 biomarker levels. The benefits of dupilumab were consistently observed in the overall population and in participants with potentially higher morbidity and mortality outcomes and in the former and current smoker populations. Question for the clinical expert: What would be considered an absence of clinical benefit or loss of response?
☐	**b) Treatment interruptions** Example: If there is progression during a "drug holiday", can treatment be resumed? According to what timeframe?
☐	**c) Definition of fixed-duration therapy** Example: Should therapy end after x number of doses or after two years, whichever comes first?
☐	**d) Consistency with discontinuation criteria associated with other drugs reviewed by CADTH in the same therapeutic space** Example: Consider alignment with stopping criteria for drug B.
2.5 CONSIDERATIONS FOR PRESCRIBING OF THERAPY Check any category where you have identified potential or current **issues** and provide brief details	
☐X	**a) Dosing, schedule/frequency, dose intensity** For info – Dosing: 300mg SC q2w
☐	**b) Drug administration** Example: Intrathecal administration requires special training and facilities.
☐X	**c) Concerns related to accessing clinical specialists and/or special settings** For Info: Per sponsor, both spirometry and blood eosinophil tests are widely available across Canada. However, spirometry is only performed in specialty respiratory clinics or hospitals and therefore there may be limitations in accessing this test for some patients.
☐	**d) Concerns related to combination usage** Example: The combination includes an oral and an IV drug that would be reimbursed through different programs.
☐	**e) Consistency with prescribing criteria associated with other drugs reviewed by CADTH in the same therapeutic space** Example: Consider alignment with prescribing criteria for drug B.

Table 3: Special Implementation Issues

2.6 GENERALIZABILITY Check any category where you have identified potential or current **issues** and provide brief details	
☐	**a) Populations of interest matching the indication but with insufficient data** Example: Patients with ECOG performance status >1 were excluded from the trial. Can they be considered eligible?
☒	**b) Populations outside the indication or reimbursement request but of interest to jurisdictions** Question for the expert: Could dupilumab be considered in patients with uncontrolled COPD who do not have type 2 inflammation?
☐	**c) Patients on active treatment with a time-limited opportunity to switch to the drug(s) under review** Example: Potential need to allow switching patients currently receiving a comparator, if the drug under review is recommended and deemed superior.
2.7 FUNDING ALGORITHM (ONCOLOGY ONLY) Check any aspect that may require the development of a provisional funding algorithm by CADTH	
☐	Drug may change place in therapy of comparator drugs
☐	Drug may change place in therapy of drugs reimbursed in previous lines
☐	Drug may change place in therapy of drugs reimbursed in subsequent lines
☐	Complex therapeutic space with multiple lines of therapy, subpopulations, or competing products
☐	Other aspects:
2.8 CARE PROVISION ISSUES Check any category where you have identified potential or current **issues** and provide brief details	
☐	**a) Drug preparation, storage, administration or dispensing** Example: Drug needs to be initiated in the hospital setting while maintenance therapy would be provided in the community setting.
☐	**b) Management of adverse effects** Example: Tumour lysis syndrome needs to be monitored and managed in the hospital.
☐	**c) Additional supportive medication or other health interventions** Example: Immunosuppressive drug requires co-administration of prophylactic antimicrobials.
☐	**d) Companion diagnostics (e.g., access issues, timing of testing)** Example: Need advice on optimal timing of biomarker testing (e.g., at time of diagnosis, as part of eligibility assessment prior to initiation).
☐	**e) Other care provision issues** Example: To manage toxicity, can one drug of the pair be stopped and the other continued until loss of clinical benefit?
2.9 SYSTEM AND ECONOMIC ISSUES Check any category where you have identified potential or current **issues** and provide brief details	
☒	**a) Concerns regarding the anticipated budget impact and sustainability** In the base case analysis, DUPIXENT is associated with 1.20 QALY gains and an incremental cost of $78,249 per person, over their lifetime, versus background therapy alone. This equates to an estimated incremental cost-effectiveness ratio of $65,207 per QALY gained. Sensitivity analyses showed that DUPIXENT remained cost-effective when varying key model parameters and under many different structural assumptions. A budget impact analysis (BIA) reflecting a pan-Canadian (excluding Quebec) drug program perspective was conducted to determine the incremental budget impact to public payers if DUPIXENT is funded as an add-on to background therapy. Assuming DUPIXENT could be

	funded in July 2026, the BIA estimates that there will be 2,669 patients in Year 1, 6,924 patients in Year 2, and 11,918 patients in Year 3 treated with DUPIXENT. Based on the assumptions used in the base case analysis, the cumulative 3-year incremental costs to Canadian public payers with the addition of DUPIXENT was estimated to be $549,243,655.
☐	**b) Additional costs to be considered (other than related to care provision as detailed above)** Example: This therapy requires facilities that are not available in all provinces. Drug plans may need to cover travel expenses for eligible patients.
☐	**c) Involvement of additional payers** Example: The implantable device component of this therapy will need to be funded by medical services departments within jurisdictional health care systems.
☐	**d) Presence of confidential negotiated prices for comparators** Example: Comparators A and B have successfully gone through price negotiations for the same indication.
☐	**e) Special programs or initiatives for the introduction and management of the drug(s) under review** Example: Due to their abuse potential, drugs of this class are usually subjected to a controlled distribution program.
☐	**f) Other system or economic issues** Example: High upfront cost of this gene therapy may require special payment arrangements.