Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

Proposed Project Scope

Long-Acting Inhaled Drugs for Chronic Obstructive Pulmonary Disease

Date: December 2024

Background and Rationale

Clinical Context and Technology

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airway obstruction, inflammation, limited expiratory flow with subsequent lung hyperinflation, and increasing frequency and severity of exacerbations. The cause of COPD is believed to be exposure to environmental factors, with its most important risk factor being smoking. Co-morbidities, such as cardiovascular disease, are common. On average, COPD patients experience 0.5 to 3.5 exacerbations per year.[1] Acute exacerbations are associated with increased health care utilization, decrease in lung function, poor health-related quality of life, and increased mortality.

The goals of COPD treatment are to prevent exacerbations, reduce respiratory symptoms, and improve patient functioning and quality of life. COPD treatments include oral and inhaled therapies in addition to non-pharmacological interventions, such as smoking cessation, pulmonary rehabilitation, and annual influenza vaccination. Antibiotics may be indicated in acute exacerbations. The proposed project will be limited to inhaled therapies. Short-acting bronchodilators (short-acting β2 agonists [SABAs] and short-acting muscarinic antagonists [SAMAs]) are used as rescue medication (acute exacerbations) or in mild COPD, while long-acting bronchodilators (long-acting β2 agonists [LABAs] and long-acting muscarinic antagonists [LAMAs]) are the treatment of choice for patients with moderate to severe COPD or in case of treatment failure in patients with mild COPD. Inhaled corticosteroids (ICSs) are used in patients with severe COPD or with uncontrolled disease.

Patients who do not respond well to monotherapy may benefit from combination therapy. Inhalers combining ICS and LABA or LABA and LAMA are available, and triple ICS-LABA-LAMA therapies were reviewed and recommended by Canada's Drug Agency after failure of dual therapy. Inhaled therapies approved in Canada and their recommended reimbursement criteria are listed in Appendix 1.

Policy Issues

New 2023 Canadian Thoracic Society (CTS) guidelines[2] call for more aggressive treatment of COPD in moderate to severe patients, recommending upfront maintenance with LABA-LAMA. This is consistent with recent labeling changes that have removed conditions of prior failure with a single-agent bronchodilator for all dual therapy combination products, but not in line with CDEC recommendations and most jurisdictional criteria that require prior trial of a single-agent long-acting bronchodilator. In the same vein, CTS recommends upfront triple ICS-LABA-LAMA therapy in a subset of patients at high risk of exacerbation. This is not aligned with labels or drug plan policies which require prior failure with dual therapies. Conversely, CTS does not recommend ICS-LABA for any COPD patient other than those with comorbid asthma, as it is deemed less effective and-or safe than alternatives. It is suspected that ICS-LABA may be widely used, which could be suboptimal for patients. Updated reimbursement criteria for ICS-LABA may be required. Overall, reimbursement criteria for COPD drugs are inconsistent across the country. There is a need to align public reimbursement policies with the best and most recent evidence of clinical and cost-effectiveness.

Table I: Policy Questions

Item	Policy Question
1	Should LABA-LAMA combination therapy be reimbursed as initial therapy for COPD?
2	What conditions (e.g., clinical severity and prerequisite therapies) are appropriate for the reimbursement of ICS-LABA therapy for COPD?
3	Should ICS-LABA-LAMA triple therapy be reimbursed as initial therapy for moderate to severe COPD at high risk of exacerbations.

COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA= long-acting β2 agonists; LAMA = long-acting muscarinic antagonists

Project Description

The main objective of the project is to address inconsistencies between COPD pharmacotherapy guidelines, Health Canada labels, recommendations from CDA-AMC, and current evidence. A **Therapeutic Review** with Formulary Management Expert Committee (FMEC) recommendations is proposed.

The specific objectives are:

1) To define place in therapy and coverage criteria of LABA-LAMA combination therapy by examining the comparative effectiveness and safety of LABA-LAMA vs. single agent bronchodilators. This will be complemented by a cost-utility analysis to compare sequencing of LABA or LAMA followed by dual LABA-LAMA with upfront LABA-LAMA.
2) To define place in therapy of LABA-ICS combination therapy by examining the comparative effectiveness and safety of LABA-ICS vs. LABA-LAMA. Findings will be complemented by a cost-utility analysis for both drugs classes.
3) To define place in therapy and coverage criteria of ICS-LABA-LAMA combination therapy by examining the comparative effectiveness and safety of ICS-LABA-LAMA vs. dual agent bronchodilators. This will be complemented by a cost-utility analysis to compare sequencing of LABA-LAMA followed by ICS-LABA-LAMA with upfront ICS-LABA-LAMA.

The patient perspective will be used to contextualize the evidence and prioritize outcomes that are important to patients.

Table II: Research Questions

Item	
1	What is the comparative efficacy and safety of ICS-LABA-LAMA, ICS-LABA, LABA-LAMA, LABA or LAMA monotherapies, in the treatment of COPD?
2	What is the cost-effectiveness of upfront LABA-LAMA compared with LABA or LAMA therapy for COPD?
3	What is the cost-effectiveness of ICS-LABA compared with LABA-LAMA therapy for COPD?
4	What is the cost-effectiveness of upfront ICS-LABA-LAMA compared with LABA-LAMA for COPD at high risk of exacerbation?

COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA= long-acting β2 agonists; LAMA = long-acting muscarinic antagonists

Table III: Project Scope—Systematic Review with Network Meta-Analysis

Elements	In Scope
Population	Patients with COPD Subgroups: • Mild, moderate, severe, very severe COPD[a] • Risk of exacerbation (low, high)[b]
Intervention[c]	ICS-LABA-LAMA ICS-LABA LABA-LAMA Combinations with single or multiple inhalers are in scope
Comparators	Other interventions in scope Single LABA Single LAMA
Outcomes	*Efficacy outcomes* • FEV1

Elements	In Scope
	• Dyspnea (e.g., Transitional Dyspnea Index) • Annual rate of moderate or severe COPD exacerbations • ER admissions and hospitalization for COPD • Exercise (exercise tolerance, exercise capacity) • Health-related quality of life e.g., SGRQ score • Mortality (all cause, due to COPD) • Patient satisfaction-adherence *Safety outcomes* • Any AEs • Any SAEs • All withdrawals • Withdrawals due to AE • Withdrawals due to lack of efficacy • Notable AEs: pneumonia
Study type	Randomized controlled trials

AE = adverse event; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA= long-acting β2 agonists; LAMA = long-acting muscarinic antagonists SAE = serious adverse events; SGRQ = St. George's Respiratory Questionnaire; RCT = randomized controlled trial; TEAE=treatment-emergent adverse events

[a] Moderate COPD is defined as 50% ≤ FEV1 < 80% predicted. Severe COPD is defined as 30% ≤ FEV1 < 50% predicted. Very severe COPD is defined as FEV1 < 30% predicted.

[b] High risk of exacerbation is defined as ≥ 2 moderate exacerbations or ≥ 1 severe exacerbation in the last year (severe exacerbation is an event requiring hospitalization or ED visit).

[c] The review will report results by drug classes only, not single products. It is assumed that products of the same class have similar clinical efficacy and safety. This assumption will be validated by the NMA. See Appendix 1 for a list of products by drug classes.

Table IV: Project Scope—Economic Analysis

Elements	In Scope
Population	Patients with COPD Subgroups: • Mild, moderate, severe, very severe[a] • Risk of exacerbation (low, high)[b]
Intervention(s)	RQ2: Upfront LABA-LAMA dual therapy RQ3: ICS-LABA therapy RQ4: Upfront ICS-LABA-LAMA therapy
Comparators	RQ2: Upfront LABA then LABA-LAMA, upfront LAMA then LABA-LAMA RQ3: LABA-LAMA therapy RQ4: Upfront LABA-LAMA then ICS-LABA-LAMA; LABA, then LABA-LAMA, then ICS-LABA-LAMA; LAMA, then LABA-LAMA, then ICS-LABA-LAMA,
Outcomes	Cost-effectiveness ratio (ICER)
Study type	Economic study (cost-utility with Makhov model)

COPD = chronic obstructive pulmonary disease; ICER = incremental cost-effectiveness ratio; ICS = inhaled corticosteroid; LABA= long-acting β2 agonists; LAMA = long-acting muscarinic antagonists; RQ = research question

[a] Mild COPD is defined as FEV1 ≥ 80%. Moderate COPD is defined as 50% ≤ FEV1 < 80% predicted. Severe COPD is defined as 30% ≤ FEV1 < 50% predicted. Very severe COPD is defined as FEV1 < 30% predicted.

[b] High risk of exacerbation is defined as ≥ 2 moderate exacerbations or ≥ 1 severe exacerbation in the last year (severe exacerbation is an event requiring hospitalization or ED visit).

Key Project and Protocol Components

In order to address the questions described above, this Therapeutic Review project will include the following key components:

- A systematic review of the evidence on clinical efficacy and effectiveness of the drugs classes in scope. Statistical pooling of the clinical data and indirect treatment comparison, in the form of a network meta-analysis, will be performed data permitting.
    - Study design to be considered in the systematic review:
        - Randomized clinical trials
- Cost-utility analysis
    - Key features:
        - Review of published economic analyses
        - Economic model
        - Cost-utility analysis (preferred design).
- Summary of patient input (including preferences, experiences, and expectations) obtained from feedback on this document.
- A utilization analysis of COPD drugs in Canada may be conducted as a complementary project.
- FMEC recommendations addressing policy questions.
- Revisions to CDEC recommendations of COPD pharmacotherapy products, based on implications of FMEC recommendations.

Methods

An information specialist will perform the literature search for clinical studies, using a peer-reviewed search strategy according to CADTH's PRESS Peer Review of Electronic Search Strategies checklist.[3]

Published literature will be identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches will be run simultaneously as a multi-file search. Duplicates will be removed using Ovid deduplication for multi-file searches, followed by manual deduplication in EndNote. The search strategy will be comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts will be developed based on the elements of the PICOS framework and research questions. The main search concepts are COPD and long-acting inhaled therapies, including specific drug names, classes, as well as general terms for these drugs.

CDA-AMC-developed search filters will be applied to limit retrieval to randomized controlled trials. Conference abstracts will be excluded from the search results. The initial search will be limited to English-language documents published since January 1, 2000. Regular alerts will update the search until project completion.

Two reviewers will screen the titles and abstracts of the screened citations for relevance to the clinical research question. Studies will be excluded if they are in languages other than English and do not meet the selection criteria outlined in Table III. Potentially relevant studies will be retrieved, and their full text will be examined.

Status of the Document

This proposed project scope is posted for 10 business days for feedback of interested parties. The feedback will be considered as the project plan is finalized. A list of included studies and a project protocol will be posted on CDA-AMC's website.

References

1. Seemungal TA, Hurst JR, Wedzicha JA. Exacerbation rate, health status and mortality in COPD--a review of potential interventions. *Int J Chron Obstruct Pulmon Dis.* 2009;4(;):203-223.
2. Bourbeau J, Bhutani M, Hernandez P, et al. 2023 Canadian Thoracic Society Guideline on pharmacotherapy in patients with stable COPD. *Chest.* 2023;164(5):1159-1183.
3. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol.* 2016;75:40-46.

Appendix 1: Products

Table V: Long-Acting Inhalable COPD Products Available in Canada

Drug (Trade name, Manufacturers)	Dosage Form and Strength (ATC code)	Health Canada Approved Indications Related to COPD	CDA-AMC Recommendation
LABA			
Salmeterol (SereVent Diskus, GSK)	50 mcg inhalant powder (R03AC12)	long term, twice daily (morning and evening) administration in the maintenance treatment of bronchospasm and relief of dyspnea associated with COPD, including chronic bronchitis and emphysema.	N/A
LAMA			
Tiotropium (Spiriva, Boehringer Ingelheim)	Inhalation powder capsules, 18 mcg tiotropium (as tiotropium bromide monohydrate) (R03BB04)	long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.	N/A
Tiotropium (Spiriva Respimat, Boehringer Ingelheim)	Inhalation solution, 2.5 mcg per actuation (R03BB04)	as a long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and for the reduction of exacerbations.	The Canadian Drug Expert Committee (CDEC) recommends that tiotropium bromide (Spiriva Respimat) be listed for the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and for the reduction of exacerbations, if the following condition is met: Condition: • List in a manner similar to Spiriva HandiHaler.
Aclidinium (Tudorza Genuair, Covis Pharma)	400 mcg aclidinium bromide per metered dose (R03BB05)	as a long-term maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.	The Canadian Drug Expert Committee (CDEC) recommends that aclidinium bromide be listed for the treatment of chronic obstructive pulmonary disease (COPD) if the following conditions are met: Conditions: • List in a manner similar to other long-acting antimuscarinic antagonists (LAMAs). • Drug plan costs for aclidinium bromide should not exceed the cost of any other LAMA.
Glycopyrronium (Seebri Breezhaler, Novartis)	Inhalation powder hard capsules,50	as a long-term once-daily maintenance bronchodilator treatment in patients with	The Canadian Drug Expert Committee (CDEC) recommends that glycopyrronium bromide be listed

Drug (Trade name, Manufacturers)	Dosage Form and Strength (ATC code)	Health Canada Approved Indications Related to COPD	CDA-AMC Recommendation
	mcg glycopyrronium as glycopyrronium bromide per capsule (R03BB06)	chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.	for the treatment of chronic obstructive pulmonary disease (COPD) with the following condition: • List in a manner similar to tiotropium.
Umeclidinium (Incruse Ellipta, GSK)	62.5 mcg umeclidinium (as bromide) per oral inhalation (R03BB07)	for the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.	The Canadian Drug Expert Committee (CDEC) recommends that umeclidinium be listed for the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, if the following conditions are met: Conditions: • List in a manner similar to other long-acting muscarinic antagonist (LAMA) monotherapies used in the treatment of COPD • Limited to monotherapy (i.e., a fixed-dose combination [FDC] long-acting beta-antagonist [LABA]/LAMA should be used if combination therapy is required) • The drug plan cost for umeclidinium should not exceed the drug plan cost of other LAMA products used as monotherapy for COPD.
LABA-LAMA			
Indacaterol/glycopyrronium (Ultibro Breezhaler, Novartis)	110 mcg/50 mcg per capsule, Inhalation (R03AL04)	for the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, and for the reduction of exacerbations of COPD in patients with a history of exacerbations.	The Canadian Drug Expert Committee (CDEC) recommends that indacaterol maleate/glycopyrronium bromide (IND/GLY) be listed for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), if the following clinical criteria are met: Clinical Criteria: • Moderate to severe COPD, as defined by spirometry. • Inadequate response to a long-acting bronchodilator (long-acting beta-2 agonist [LABA] or long-acting anticholinergic [LAAC]).

Drug (Trade name, Manufacturers)	Dosage Form and Strength (ATC code)	Health Canada Approved Indications Related to COPD	CDA-AMC Recommendation
Umeclidinium/vilanterol (Anoro Ellipta, GSK)	62.5 mcg umeclidinium (as bromide) and 25 mcg vilanterol (as trifenatate) per oral inhalation (R03AL03)	for the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.	The Canadian Drug Expert Committee (CDEC) recommends that umeclidinium bromide/vilanterol trifenatate (UMEC/VI) be listed for the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, if the following clinical criteria are met: Clinical Criteria • Moderate to severe COPD as defined by spirometry • Inadequate response to a long-acting bronchodilator (long-acting beta-2 agonist [LABA] or long-acting anticholinergic [LAAC]).
Aclidinium/formoterol (Duaklir Genuair, Covis Pharma)	400 mcg aclidinium bromide / 12 mcg formoterol fumarate per metered dose (R03AL05)	indicated as a long-term maintenance bronchodilator treatment for airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.	The Canadian Drug Expert Committee (CDEC) recommends that aclidinium bromide/formoterol fixed-dose combination (FDC) be listed for long-term maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, if the following conditions are met: Conditions: • List in a manner similar to other long-acting muscarinic antagonist (LAMA)/long-acting beta-agonist (LABA) FDC products. • Drug plan costs for aclidinium/formoterol should not exceed drug plan costs for other listed LAMA/LABA combination products.
Tiotropium/olodaterol (Inspiolto Respimat, Boehringer Ingelheim)	2.5 mcg/2.5 mcg per actuation (R03AL06)	for the long term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with Chronic Obstructive Pulmonary Disease (COPD), including chronic bronchitis and emphysema.	The CADTH Canadian Drug Expert Committee (CDEC) recommends that tiotropium/olodaterol (TIO/OLO) be listed for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, if the following clinical criteria and condition are met: Clinical Criteria:

Drug (Trade name, Manufacturers)	Dosage Form and Strength (ATC code)	Health Canada Approved Indications Related to COPD	CDA-AMC Recommendation
			• Moderate to severe COPD as defined by spirometry • Inadequate response to a long-acting beta2 agonist (LABA) or long-acting muscarinic antagonist (LAMA). Condition: • Drug plan costs for TIO/OLO should not exceed the drug plan costs for other LAMA/LABA combination products.
ICS-LABA			
Budesonide/formoterol (Symbicort Turbuhaler, AstraZeneca)	100 mcg budesonide and 6 mcg formoterol fumarate dihydrate 200 mcg budesonide and 6 mcg formoterol fumarate dihydrate 400 mcg budesonide and 12 mcg formoterol fumarate dihydrate (R03AK07)	for the maintenance treatment of moderate to severe COPD including chronic bronchitis and emphysema, in patients with persistent symptoms and a history of exacerbations, where the use of a combination product is considered appropriate.	N/A
Fluticasone furoate/vilanterol (Breo Ellipta, GSK)	100 mcg/25 mcg (R03AK10)	for the long-term once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and to reduce exacerbations of COPD in patients with a history of exacerbations.	The Canadian Drug Expert Committee (CDEC) recommends that fluticasone furoate/vilanterol (FF/V) be listed for the long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and to reduce exacerbations of COPD in patients with a history of exacerbations, if the following clinical criteria are met: Clinical Criteria: • Moderate to severe COPD as defined by spirometry. • Inadequate response to a long-acting bronchodilator (long-acting beta-2 agonist [LABA]/long-acting muscarinic antagonist [LAMA]) or experiencing exacerbations more

Drug (Trade name, Manufacturers)	Dosage Form and Strength (ATC code)	Health Canada Approved Indications Related to COPD	CDA-AMC Recommendation
			than once per year while on a long-acting bronchodilator.
Fluticasone propionate/salmeterol (Advair, GSK)	125 mcg/25 mcg 250 mcg/25 mcg (R03AK06)	for the maintenance treatment of COPD, including emphysema and chronic bronchitis, in patients where the use of a combination product is considered appropriate.	N/A
Fluticasone propionate/salmeterol • Advair Diskus (GSK) • Wixela Inhub (Mylan) • Generic (PMS)	100/50mcg 250/50mcg 500/50mcg (R03AK06)	for the maintenance treatment of COPD, including emphysema and chronic bronchitis, in patients where the use of a combination product is considered appropriate.	N/A
ICS-LABA-LAMA			
Fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta, GSK)	100/62.5/25 mcg 200/62.5/25 mcg (R03AL08)	in adult patients who are not adequately treated by a combination of an ICS/LABA or a combination of a LAMA/LABA: for the long-term, once daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema • to reduce exacerbations of COPD in patients with a history of exacerbations	The CADTH Canadian Drug Expert Committee (CDEC) recommends that fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) be reimbursed for the long-term, once daily, maintenance treatment of COPD, including chronic bronchitis and/or emphysema, if the following criteria and condition are met: Criteria • Patients should not be started on triple inhaled therapy as initial therapy for COPD. • For use in patients who are not controlled on optimal dual-inhaled therapy for COPD. Condition • Drug plan cost of FF/UMEC/VI should not exceed the drug plan cost of treatment with any triple therapies reimbursed for COPD (long-acting muscarinic antagonist [LAMA]/long-acting beta-2 agonist [LABA]/inhaled corticosteroid [ICS]).
Budesonide/glycopyrronium/formoterol (Breztri Aerosphere, AstraZeneca)	182 mcg/8.2 mcg/5.8 mcg (R03AL11)	for the long-term maintenance treatment to reduce exacerbations of chronic obstructive pulmonary disease (COPD) and treat airflow obstruction in patients with COPD, including chronic bronchitis	The CADTH Canadian Drug Expert Committee (CDEC) recommends that budesonide/ glycopyrronium/formoterol (BGF) should be reimbursed for the long-term maintenance

Drug (Trade name, Manufacturers)	Dosage Form and Strength (ATC code)	Health Canada Approved Indications Related to COPD	CDA-AMC Recommendation
		and/or emphysema who are not adequately treated by a combination of an ICS/LABA or a combination of a LAMA/LABA.	treatment of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/ or emphysema, only if the conditions listed in Table 1 are met. 1. Reimburse In a similar manner to FF/UMEC/VI. 2. BGF should not exceed the drug program cost of treatment with the least-costly fixed-dose ICS/LAMA/ LABA triple therapy combination reimbursed for the long-term maintenance treatment of COPD including chronic bronchitis and/or emphysema.

ATC = Anatomical Therapeutic Chemical, COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA= long-acting β2 agonists; LAMA = long-acting muscarinic antagonists; N/A = not available