Long Acting Muscarinic Antagonists (LAMA) for the Treatment of Chronic Obstructive Pulmonary Disease (COPD)

Final Consolidated Report

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ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Ontario Drug Policy Research Network

The Ontario Drug Policy Research Network (ODPRN) is funded to conduct drug class reviews as part of an initiative to modernize the public drug formulary in Ontario. As such, the ODPRN works closely with the Ontario Public Drug Programs (OPDP), Ministry of Health and Long-Term Care to select key priority areas and topics for formulary modernization, then conducts independent drug class reviews and disseminates the results of each of these reviews directly to the OPDP to facilitate informed decision making on public drug funding policies.

Conflict of Interest Statement

Muhammad Mamdani was a member of an advisory board for Hoffman La Roche, Pfizer, Novartis, GlaxoSmithKline and Eli Lilly Canada.
Paul Oh was a member of an advisory board for Amgen, Astra Zeneca, Janssen, Novartis, Pfizer, Roche and Sanofi.
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No other study members report any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that may present a potential conflict of interest in the LAMA for COPD Drug Class Review.

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Study Team

- Formulary Modernization Team: Paul Oh, Sandra Knowles
- Qualitative Team: Julia E. Moore, Sobia Khan, Alekhya Mascarenhas, and Marlon Rhoden from the Knowledge Translation Program at the Li Ka Shing Knowledge Institute
- Systematic Review Team: Andrea C. Tricco, Lisa Strifler, Fatemeh Yazdi, Paul Khan, Carmen Ng, Jesmin Antony, Kelly Mrklas, Alistair Scott, Jennifer D'Souza, Roberta Cardoso, Sharon E. Straus
- Pharmacoepidemiology Team: Tara Gomes, Andrea Gershon, Matthew Stanbrook, Ximena Camacho, Diana Martins, Samantha Singh, Zhan Yao, Michael Paterson, David Juurlink and Muhammad Mamdani
- Pharmacoeconomics Team: Doug Coyle, Karen Lee, Kelley-Anne Sabarre, Kylie Tingley, Kathryn Coyle
- Research Team, Clinical Experts: Matthew Stanbrook, Tony D'Urzo
- Research Team, Patient Representative: Theresa Bujtas
- Research Team, Representative from Committee to Evaluate Drugs: Anne Holbrook

Note

Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

List of Abbreviations

BC	British Columbia
BFC	Budesonide + formoterol combination
CDR	Common Drug Review
CED	Committee to Evaluate Drugs
CHMS	Canadian Health Measures Survey
CIHI	Canadian Institute for Health Information
COPD	Chronic obstructive pulmonary disease
CrI	Credible interval
DPI	Dry powder inhaler
EAP	Exceptional Access Program
ED	Emergency department
FEV1	Forced expiratory volume in 1 second
FSC	Fluticasone + salmeterol combination
FVC	Fluticasone + vilanterol combination
ICES	Institute for Clinical Evaluative Sciences
ICS	Inhaled corticosteroid
ICS+LABA	ICS+LABA combination products
LABA	Long-acting beta-agonist
LAMA	Long-acting muscarinic antagonist
LAMA+LABA	Long-acting muscarinic antagonist + long-acting beta-agonist
LAMA+ICS+LABA	Long-acting muscarinic antagonist + inhaled corticosteroid + long-acting beta-agonist
LU	Limited Use
MDI	Metered dose inhaler
MFC	Mometasone + formoterol combination
MOHLTC	Ministry of Health and Long-term Care
NIHB	Non-insured Health Benefits
NNH	Number needed to harm
NNT	Number needed to treat
NT	Northwest Territories
NU	Nunavut
ODB	Ontario Drug Benefit
ODPRN	Ontario Drug Policy Research Network
OPDP	Ontario Public Drug Programs
PEF	Peak expiratory flow
PEI	Prince Edward Island
QALY	Quality adjusted life year
RCT	Randomized controlled trial
SABA	Short-acting beta-agonist
SAMA	Short-acting muscarinic antagonist
SGRQ	St. George's Respiratory Questionnaire
SMH	St. Michael's Hospital
US	United States
WHO	World Health Organization

Executive Summary

In Canada, there are three long-acting muscarinic antagonist (LAMA, also known as anticholinergic) products available: tiotropium (Spiriva), glycopyrronium bromide (Seebri Breezhaler) and aclidinium (Tudorza). These products are indicated solely for the management of patients with chronic obstructive pulmonary disease (COPD). There are two LAMA+long-acting beta-agonists (LABA) combination products for the management of patients with COPD that were introduced onto the Canadian market in 2014: indacaterol + glycopyrronium (Ultibro) and vilanterol + umeclidinium (Anoro Ellipta). In Ontario, tiotropium, aclidinium and glycopyrronium bromide are available through a general benefit listing on the Ontario Drug Benefit (ODB) formulary with a therapeutic note. The LAMA+LABA combination products are not currently listed in Ontario.

As part of the formulary modernization review, an evaluation of LAMA products (including LAMA+LABA combination products) for the management of patients with COPD was undertaken. Detailed information for each of the reports can be found on the ODPRN website.

Key Considerations for Reimbursement Options

Efficacy and Safety

A systematic review was conducted to examine the available evidence with respect to clinical outcomes for therapies commonly used to treat COPD. No statistically significant differences in exacerbations between the individual LAMA agents were observed for patients with moderate COPD. In this population, LAMA products were found to be more effective than LABAs for the reduction of any exacerbations. However, individual LAMAs products were found to be inferior to inhaled corticosteroids (ICS) +LABA combination products. For the comparison of LAMAs vs LAMA+ICS+LABA ("triple therapy"), there was insufficient data to draw meaningful conclusions. Although no statistically significant differences were observed for LAMAs vs LAMA+ICS+LABA ("triple therapy") with respect to exacerbations, this finding may be due to a lack of evidence to detect a true difference between the agents; only two trials including 756 patients provided direct evidence on this treatment comparison.

For LAMA+LABA combination products, no statistically significant difference was noted for exacerbations in comparison to individual LAMAs, ICS+LABAs or LAMA+ICS+LABAs. Note that for the LAMA+LABA versus ICS+LABA and LAMA+LABA versus LAMA+ICS+LABA results, there was insufficient data to draw meaningful conclusions as only one trial provided direct evidence on each of these treatment comparisons. Compared to LABA alone, LAMA+LABA decreased the risk of exacerbation.

For the safety outcome of arrhythmias, no statistically significant differences were observed across any of the LAMA or LAMA+LABA comparisons. In contrast, LAMAs (i.e., glycopyrronium and tiotropium) had a lower risk of pneumonia compared with ICS+LABA. For the safety outcome of cardiovascular-related mortality, no significant differences were observed except for an increase in risk for patients treated with tiotropium when compared to LABA or ICS+LABA.

Accessibility

LAMAs are currently available as a general benefit in Ontario for patients qualifying for Ontario Public Drug Programs (OPDP), including those 65 years and older. No accessibility issues were identified in our review. However, for patients under the age of 65 and without public or private coverage, access to COPD medications including LAMAs may be a challenge as LAMAs cost approximately $60/month, and monthly costs of ICS+LABA products range from approximately $87-145/month.

Pharmacoeconomics

The de novo economic evaluation found that LAMA monotherapies were cost effective when compared to ICS single agents and Serevent (salmeterol), but not to Oxeze (formoterol) at the listed drug prices. Further, the analysis did not find LAMA+LABA combination therapies cost-effective when compared to Symbicort (budesonide+formoterol) at the listed drug prices. Triple therapy (i.e., LAMA plus ICS+LABA) was not cost-effective compared to ICS+LABA combination therapies at listed prices. As noted above, for the comparison of LAMAs vs LAMA+ICS+LABA ("triple therapy"), there was insufficient data to draw meaningful conclusions; any uncertainty in our NMA would affect the results of the pharmacoeconomic analyses. Assuming a willingness to pay of $50,000 per QALY, it may not be cost effective to fund either LAMA+LABA combination product (Ultibro or Anoro Ellipta) if there is an inability to negotiate a price reduction. However, if a price reduction of at least 29% relative to its currently listed price can be negotiated, reimbursement of Ultibro for patients with at least moderate disease would be optimal.

If LAMA+LABA combination products are listed as a general benefit at currently listed prices, an increase in total expenditure on COPD therapy would be approximately 17%. A sensitivity analysis whereby the number of units of LAMA+LABA products was based on previous use of LAMA and ICS+LABA products forecasted a smaller budget increase of less than 1%. Negotiating a 25% price reduction with both LAMA+LABA products would lead to a small reduction in OPDP expenditure (approximately $2.5 million annually).

Reimbursement Options

Final recommendations for the funding of LAMAs for COPD through the publicly funded drug program in Ontario will be made upon completion of the Social Acceptability Research (Citizen's Panel led by the Qualitative Research Team) and the Stakeholder Review that will be conducted after completion of ICS+LABA for asthma drug class review.

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Rationale for Review

In Canada, there are three LAMA products available: tiotropium (Spiriva), glycopyrronium bromide (Seebri Breezhaler) and aclidinium (Tudorza). These products are indicated solely for the management of patients with COPD. There are two LAMA+LABA combination products for the management of patients with COPD that were introduced onto the Canadian market in 2014: indacaterol + glycopyrronium (Ultibro) and vilanterol + umeclidinium (Anoro Ellipta).

In Ontario, all three LAMA products are available as general benefits on the ODB formulary with a therapeutic note. The LAMA+LABA combination products are currently being reviewed by the Common Drug Review (CDR), and are not currently listed in Ontario.

As LAMAs are often used in combination with ICS+LABA (i.e., "triple therapy") for the management of patients with moderate to severe COPD, an evaluation of LAMA products (including LAMA+LABA products) as well as ICS+LABA combination products for the management of patients with COPD (and asthma) was undertaken to provide funding and policy recommendations of these products in Ontario.

This report outlines the key findings for each of the components of the review. More detailed information for each of the reviews can be found on the ODPRN website.

Background Information

COPD is a common and debilitating lung disease that is characterized by progressive airflow obstruction (partially reversible), inflammation in the airways and systemic effects.[1] COPD is presently the fourth leading cause of death worldwide, but WHO predicts that by 2030 it will become the third leading cause of death.[2] Cigarette smoking is the principal underlying cause of COPD, and quitting has been associated with improved lung function, reduced chronic cough and a decreased mortality from COPD.[1;3]

The worldwide prevalence of COPD is estimated to be more than 10% among adults aged 40 years and older.[4] In Ontario, there are 850,000 people aged 35 and older (11.8% of the population 35 years and older) diagnosed with COPD.[5] In an Ontario study, the prevalence of COPD increased from 7.8% in 1996 to 9.5% in 2007, which was a 23.0% relative increase ($p<0.001$).[6] However, approximately 60-85% of patients, mainly with mild to moderate disease, are thought to remain undiagnosed, as many patients may only seek treatment when symptoms are severe.[7] Canadian data indicated similar findings for underdiagnosis of COPD. Among Canadians aged 35 to 79 years, 4% reported having been diagnosed by a health professional with COPD, chronic bronchitis or emphysema.[8] However, spirometry data collected by the Canadian Health Measures Survey (CHMS) revealed that 13% of Canadians aged 35 to 79 had a forced expiratory volume in 1 second (FEV1)/forced vital capacity ratio less than 0.70 (measured airflow obstruction consistent with COPD). This is more than 3 times greater than the self-reported diagnosis of COPD of 4%. Although asthma and COPD are different respiratory diseases, asthma and COPD may coexist; up to 25% of adult patients with obstructive airway diseases have manifestations of both diseases, termed the asthma-COPD overlap.[5;9;10]

The burden of COPD in Canada is significant. The Canadian Institute for Health Information (CIHI) showed that COPD accounted for the highest rate of hospital admission among major chronic illnesses in Canada in 2008.[11] In addition, approximately one in five patients with COPD (18.8%) were readmitted to acute inpatient care within 30 days of discharge; of these patients, the most frequent condition upon readmission was the same condition as the index case (56% were treated for COPD symptoms).[12] Using data from Ontario, people with COPD had rates of hospitalizations, emergency room visits and ambulatory care visits that were 63%, 85% and 48% higher than the rest of the population, respectively.[5] COPD exacerbations are the major drivers for COPD morbidity and mortality, as well as the most important component for direct healthcare costs (e.g., acute care services, hospitalization).[13] In addition to the burden on the healthcare system, patients with COPD have a high symptom burden.[14] In particular, patients with advanced COPD have symptoms that are comparable to those patients with cancer or congestive heart failure.[15] COPD has a major impact on healthcare costs, lost productivity, absenteeism and presenteeism in the workplace.[16;17]

Treatment strategies

Management strategies for patients with COPD include smoking cessation, drug therapy, educational programs, pulmonary rehabilitation and maximizing use of vaccinations (i.e., pneumococcal and influenza vaccines).[18] Treatment goals are to prevent disease progression, relieve symptoms, improve exercise tolerance and prevent exacerbations. Smoking cessation is the most important factor in slowing the progression of COPD.[19] Drug therapy includes use of a bronchodilator to control symptoms with use of inhaled corticosteroid (ICS) in patients with more severe disease.[1] Bronchodilators are the cornerstone of treatment for patients with COPD and include beta-agonists (short-acting and long-acting: SABA and LABA) and muscarinic antagonists (also known as anticholinergics; short-acting and long-acting: SAMA and LAMA). Inhaled corticosteroids are generally used in combination with a long-acting bronchodilator for management of patients with moderate to severe COPD.[19] For patients with moderate to severe COPD with persistent symptoms and a history of exacerbations, a combination of LAMA plus a LABA and ICS therapy has been recommended (i.e., triple therapy").[19]

In Canada, there are three LAMA products available: tiotropium (Spiriva), glycopyrronium bromide (Seebri Breezhaler) and aclidinium (Tudorza). These products are indicated solely for the management of patients with COPD. Another single LAMA, umeclidinium (Incruse Ellipta) has received its notice of compliance (NOC) from Health Canada in April 2014 for the management of patients with COPD but is not yet available. There are two LAMA+LABA combination products for the management of patients with COPD that were introduced onto the Canadian market in 2014: indacaterol + glycopyrronium (Ultibro) and vilanterol + umeclidinium (Anoro Ellipta). All products are available as dry powder inhalers. There are currently no generic products available.

Public plan reimbursement of LAMA products in Canada

In Ontario, tiotropium (Spiriva), aclidinium (Tudorza) and glycopyrronium (Seebri) are available as general benefits. Across Canada, all public plans provide coverage for at least one LAMA product. Nine of the 12 (75%) public drug programs in Canada list LAMA products on a restricted basis for the treatment of COPD, requiring special authorization. In three provinces (Alberta, Ontario and Quebec),

LAMAs are listed as general benefits.

Restriction criteria vary among the public drug plans including spirometry results for confirmation of COPD (2 plans), prior use of SABA and/or SAMA (7 plans) OR if no trial of short-acting agents, then spirometry results (4 plans).

Exhibit 1: Public plan listings in Canada for LAMA products

Drug		BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL	YK	NIHB/ NU/ NT
LAMA single entity products													
Glycopyrronium bromide	Seebri Breezhaler	Res	Ben	Res	Res	Ben†	Ben	Res	Res	Res	Res	Res	Res
Tiotropium	Spiriva	Res	Ben	Res	Res	Ben†	Ben	Res	Res	Res	Res	Res	Res
Aclidinium bromide	Tudorza	Res	Ben	Res	No	Ben†	Ben	Res	Res	Res	Res	Res	No
LAMA + LABA combination products*													
Glycopyrronium + indacaterol	Ultibro Breezhaler	No	No	No	No	No	No	No	No	No	No	No	No
Umeclidinium + vilanterol*	Anoro Ellipta	No	No	No	No	No	No	No	No	No	No	No	No

No=not listed; Res=restricted listing – enforced; Ben=unrestricted listing

*Common Drug Review (CDR) recommendations for Ultibro available December 2014. At the time of this report, CDR recommendations for Anoro Ellipta were not yet available.

†Therapeutic note for all anticholinergic agents: Anticholinergic agents should be used with extreme caution in the elderly due to age- related central nervous system adverse effects (e.g., confusion, paranoia, hallucinations). Avoid in patients with dementia as drug-induced memory impairment is common. (This does not apply to ipratropium bromide).

Objective

The objective of the LAMA drug class review is to provide evidence-informed recommendations for the funding of LAMA products for COPD through the publicly funded drug program in Ontario. ICS+LABA for COPD and ICS+LABA for asthma are also being reviewed by ODPRN as separate drug class reviews. Due to overlapping themes, final policy recommendations for all three drug classes will be released upon completion of the three reviews.

Components of the Drug Class Review

The LAMA for COPD drug class review is comprised of:

- qualitative analyses of the perspectives of patients, pharmacists and prescribers
    - one-on-one semi-structured telephone interviews regarding specific experiences and perceptions relevant to funding policies for LAMA for COPD
- environmental scans of:
    - national and international drug policies
    - considerations relating to health equity,

- analysis of real-world drug utilization using:
    - administrative claims data from Ontario and across Canada
    - summaries of relevant observational literature,
- systematic review of the literature and network meta-analysis,
- reimbursement-based economic analyses and cost-effectiveness analysis.

Results from all of the above components were reviewed and consolidated into a set of reimbursement options for potential drug reimbursement models.

Overview of Findings

Qualitative Research Team: Perspectives of Patients and Healthcare Providers

Patient Impact of COPD

Patients with COPD may experience symptoms such as shortness of breath, coughing and excessive mucous production. Many participants in the qualitative study noted a significant decline in their ability to engage in physical activity over time, but report attempting to remain active by making adjustments to the type and pace of activities performed in order to relieve symptoms but also to maintain normality. Adaptations included having to adjust workload, workflow or being unable to work, and giving up certain hobbies due to either physical exertion or environmental factors (Qualitative Team Report).

Many patients described the toll that COPD has taken on their mental health, with stress, anxiety and depression being common. Patients perceived that their COPD has caused their family members and caregivers to experience stress and anxiety as well. Family members often provide daily support to ensure that medications are adhered to and activities of daily living can be performed. Caregivers for patients with severe COPD may have drastic life changes as a result of disease progression.

> *"My work has accommodated me that I work in an office where parking is very close now, so that's wonderful. Especially for hot days and cold windy days, so I have to consider what the weather is going to be. And when I am working, I have to think about how much I'm, how much of a load can I carry into a school, can I use a cart, is there stairs, is there meetings upstairs, you know we have one school where there's three floors and I just dread it when, oh, the meeting's on the third floor, there's no elevator, it's a really old school. So it's a constant for me, it's always on the back of my mind, how is this going to affect my breathing." - Patient*

Challenges in treating COPD

COPD therapies are perceived to be useful for preventing exacerbations, but may not lead to marked improvements in quality of life, which is an important outcome from the patients' perspective. As part of an interview follow-up, patient participants were asked to rank the relative importance of COPD outcomes in a survey. The top ranked outcomes were (in order): quality of life, shortness of breath, functional abilities and mortality.

Physician decision-making processes for prescribing COPD medications included level of evidence, guidelines, patient history with disease, prior treatment history, and ease of use in order to maximize patient adherence. All participant groups generally perceived LAMAs to be effective with minimal side effects; these factors may enhance perceptions of appropriateness and encourage patient compliance. Participants from all groups found it challenging to comment specifically on the effectiveness of this group of drugs because many patients take these in conjunction with other products such as ICS+LABAs. Few patients experience any barriers to accessing their LAMA prescriptions as most are ODB-eligible based on age criteria.

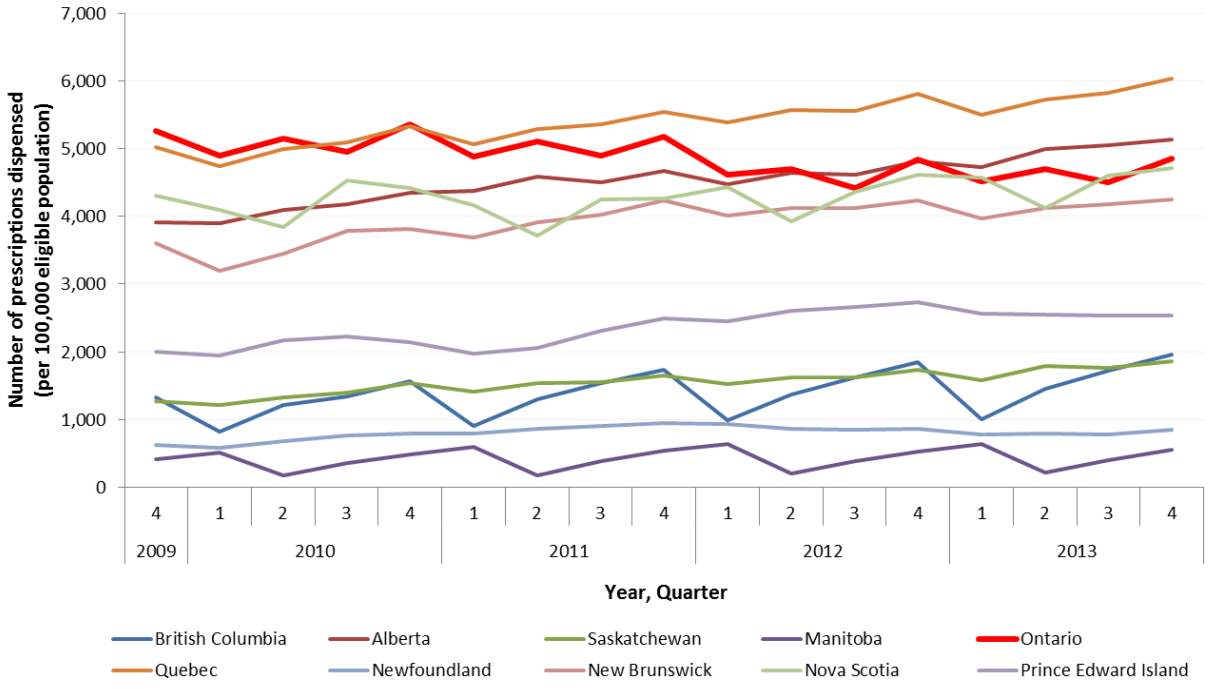
> *"I am on Spiriva and Symbicort and have COPD. These long acting meds at my present dosages are fairly effective, I think. It is difficult to compare long-term as I smoked until November 2011. Stopping smoking had been the primary indicator for me as I have fewer exacerbations since I quit smoking and no hospitalizations since, but quite a few before then." – Patient*

Pharmacoepidemiology Team

Current Utilization in Canada and Ontario

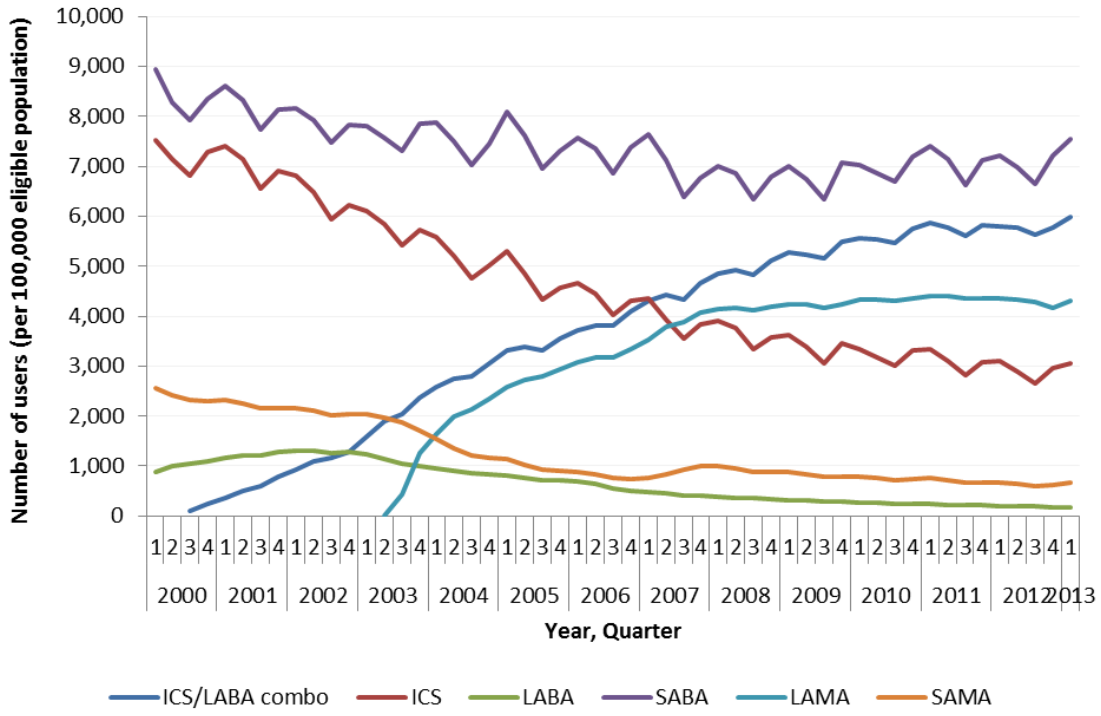
LAMA products are the fourth most commonly prescribed inhaled anti-inflammatory/bronchodilator therapies in Canada, with 536,148 prescriptions dispensed in the fourth quarter (Q4: October to December) of 2013 (Exhibit 2). Nearly all (97.4%; 522,227 prescriptions; Q4 2013) prescriptions for LAMA products dispensed in Canada were for tiotropium; glycopyrronium and aclidinium have only been available commercially since 2013 and as such, data for these drugs is limited. Ontario has the third-highest utilization rate of provincially-funded LAMA products with 4,874 prescriptions dispensed per 100,000 eligible population compared to the national average of 3,275 prescriptions per 100,000 eligible population in Q4 2013. Note that variation in the rates does not take into account differences that may exist in the average age of eligible patients between provinces. Over 80% of prescriptions for LAMAs dispensed in Ontario are paid through the Ontario Public Drug Program (OPDP) (Pharmacoepidemiology Team Report).

Exhibit 2: Population-adjusted utilization of provincially funded LAMA products in Canada, by province



Use of LAMAs increased markedly following their listing on the Ontario public drug formulary in 2003, reaching 4,303 per 100,000 beneficiaries in Q1 2013 (see Exhibit 3). Despite the steep uptake, LAMA use has plateaued in Ontario since the last quarter of 2007. There was a corresponding decrease in short-acting anti-muscarinic agents (SAMAs) following the introduction of LAMAs. SAMA use dropped 64.7% between the third quarter of 2003 (189 per 100,000 beneficiaries) and the first quarter of 2013 (663 per 100,000 beneficiaries).

Exhibit 3: Rate of use of inhaled respiratory therapies among public drug plan beneficiaries in Ontario for all indications



In 2012, 112,649 COPD patients received provincially-funded LAMA products in Ontario, almost one-quarter (27,131; 24.1%) of whom were new users. COPD patients prescribed LAMA products through the OPDP were typically over 65 years of age (N=93,218; 82.8%) and had moderate COPD severity (N=67,779; 60.2%). Just over half of COPD patients who were new users of a LAMA were treated with only a LAMA product; less than 10% were treated with concurrent single-agent ICS or LABA product ("dual therapy"), and slightly less than 40% were treated with a LAMA in addition to both ICS and LABA products (either as single-agents or ICS+LABA combination therapy; "triple therapy").

In fiscal year 2012, 51,255 (37.5%) of LAMA users had both COPD and asthma, 68,615 (50.3%) of LAMA users had only COPD, 4,871 (3.6%) of LAMA users had only asthma, and 11,765 (8.6%) of LAMA users had no indication of COPD or asthma. Although LAMAs are not indicated in patients with asthma, there is some evidence that tiotropium added to standard therapy in patients with uncontrolled moderate to severe asthma may improve lung function, as measured by peak expiratory flow (PEF) and FEV1.[20-22]

Adherence

Although pharmacotherapy is effective in controlling symptoms and maintaining lung function, research has suggested that poor adherence can lead to higher rates of exacerbation leading to hospital admission in patients with COPD.[23] One cohort study found that adherence to tiotropium (both when used alone and in combination with FSC) is moderate, with approximately two-thirds of patients being compliant to therapy over a mean 22 months follow-up. Furthermore, adherence to tiotropium therapy

was associated with reduced risks of COPD exacerbations. Among those treated with tiotropium alone, compliance to therapy was associated with reduced risks of moderate (OR, 95% CI: 0.57, 0.53 to 0.61) and severe (OR, 95% CI: 0.77, 0.72 to 0.83) exacerbations. [24]

The findings of our analysis in Ontario found that among ODB-eligible COPD patients initiating single LAMA therapy, almost half of the patients received only one prescription before discontinuing therapy. Among patients with more than one LAMA prescription, adherence to triple therapy was higher compared to dual therapy and single therapy ($p<0.0001$). Among the dual therapy users, patients were more adherent to LABA plus LAMA therapy compared to ICS plus LAMA therapy ($p=0.0002$). Along with higher adherence, triple therapy users had more severe disease compared to dual and single therapy users (20-30% and 10-20% with very severe COPD, respectively).

Rapid Review Team

Efficacy

Outcome measures used for assessment of treatment options in COPD include measures of lung function (e.g., forced expiratory volume in one second [FEV1]), symptoms (e.g., exacerbations) and patient-related endpoints (e.g., disease-specific questionnaires such as the St. George's Respiratory Questionnaire [SGRQ]). Two efficacy outcomes were used for analysis in our report: COPD exacerbations (main efficacy outcome) and mortality (secondary efficacy outcome) (Rapid Review Team Report).

Exacerbations

In our review, ninety-two randomized controlled trials (RCTs) reported on overall exacerbations and included 64,341 patients with all severities of COPD. A network meta-analysis was completed for all severity of COPD disease but inconsistency was present statistically; therefore, the sub-network meta-analysis for exacerbations for moderate COPD patients was conducted. The network was comprised of 68 RCTs that included 53,412 people (see Exhibit 4).

For all comparisons, no statistically significant differences were observed (including LAMA vs LAMA; LAMA vs. LAMA+LABA, LAMA vs. LAMA+ICS+LABA; LAMA+LABA vs. ICS+LABA; LAMA+LABA vs. LAMA+ICS+LABA) for exacerbations for patients with moderate COPD except for the following:

LAMA vs. placebo

- Compared with placebo, there was a significant decrease in risk of COPD exacerbation for those patients treated with glycopyrronium (NNT 15) or tiotropium (NNT 15).

LAMA vs. LABA

- Tiotropium had a lower risk of exacerbation relative to indacaterol (NNT 21).

LAMA vs. ICS+LABA

- Glycopyrronium had a higher risk of exacerbation compared with BFC (NNH 9) and MFC (NNH 10). Similarly, tiotropium had a higher risk of exacerbation relative to BFC (NNH 10) and MFC

(NNH 10).

LAMA+LABA vs. LABA

- Tiotropium+formoterol (not available in Canada as a combination product) had a lower risk of exacerbation relative to indacaterol alone (NNT 6) or salmeterol alone (NNT 7). Tiotropium+indacaterol (not available in Canada as a combination product) had a lower risk of exacerbation relative to indacaterol alone (NNT 11).

For the comparison of LAMAs vs LAMA+ICS+LABA ("triple therapy"), there was insufficient data to draw meaningful conclusions. Although no statistically significant differences were observed for LAMAs vs LAMA+ICS+LABA ("triple therapy") with respect to exacerbations, this finding may be due to a lack of evidence to detect a true difference between the agents; only two trials including 756 patients provided direct evidence on this treatment comparison.

For LAMA+LABA combination products, no statistically significant difference was noted for exacerbations in comparison to individual LAMAs (tiotropium vs tiotropium plus formoterol in 1 trial with 428 patients; tiotropium vs tiotropium plus salmeterol in 1 trial with 305 patients and tiotropium vs tiotropium plus indacaterol in 2 trials with 2273 patients), ICS+LABAs (fluticasone plus salmeterol vs indacaterol plus glycopyrronium in 1 trial with 422 patients), or LAMA+ICS+LABAs (tiotropium plus salmeterol vs tiotropium plus fluticasone plus salmeterol in 1 trial with 293 patients). The LAMA+LABA versus ICS+LABA and LAMA+LABA versus LAMA+ICS+LABA results should be interpreted with caution because only 1 trial provided direct evidence on each of these treatment comparisons.

Results of our ranking analysis for exacerbations for patients with moderate COPD

Of all the drugs compared, BFC, tiotropium+formoterol (not available in Canada as a combination product), MFC, GSK961081 (not available in Canada) and formoterol alone had the largest probability of being the most effective for decreasing risk of COPD exacerbation in patients with moderate COPD with a probability of 86%, 85%, 83%, 79% and 67%, respectively.

Exhibit 4: Results of meta-analysis and network meta-analysis for risk of exacerbation with moderate COPD

Intervention	Comparison	NNT
LAMA vs. placebo		
Glycopyrronium	Placebo	15
Tiotropium	Placebo	15
LAMA vs. LABA		
Tiotropium	Indacaterol	21
Tiotropium	Salmeterol	25
LAMA vs. ICS+LABA		
Glycopyrronium	Budesonide + formoterol	9 (NNH)
Glycopyrronium	Mometasone + formoterol	10 (NNH)
Tiotropium	Budesonide + formoterol	10 (NNH)
Tiotropium	Mometasone + formoterol	10 (NNH)
LAMA+LABA vs. placebo		
Tiotropium + formoterol	Placebo	6
Tiotropium + indacaterol	Placebo	9
LAMA+LABA vs. LABA		
Tiotropium + formoterol	Indacaterol	6
Tiotropium + indacaterol	Indacaterol	11
Tiotropium + formoterol	Salmeterol	7
LAMA+ICS+LABA vs. placebo		
Tiotropium + fluticasone + salmeterol	Placebo	10

Note: NNT calculated using the odds ratio from the meta-analysis whenever network meta-analysis was not statistically significant. NNT means statistically significant benefit for the first inhaler versus the comparator. NNH means statistically significant harm for the first inhaler versus the comparator (i.e., the comparator is superior to the first inhaler).

Mortality

A total of 79 RCTs including 140,849 patients, reported on mortality overall and were included in the network meta-analysis. There was no statistically significant heterogeneity or inconsistency in the

network as a whole.

For all comparisons, no statistically significant differences were observed except for ICS+LABA vs. placebo. For this comparison there was a significant decrease in risk of death for patients treated with FSC (NNT 99).

Results of our ranking analysis for mortality
Of all the drugs compared, FSC, glycopyrronium, AZD3199 (not available in Canada), MFC and aclidinium had the largest probability of being the most effective for decreasing risk of mortality with a probability of 73%, 71%, 70%, 68% and 68%, respectively.

Review of Other Studies

Exacerbations

Observational studies: Overall, limited evidence suggests that tiotropium use may be associated with lower risk of COPD exacerbations (defined as addition of oral steroids or short-term antibiotics) compared to use of the combination of ipratropium+salbutamol;[25] however there does not appear to be a reduction in hospital readmissions associated with tiotropium use following a hospitalization compared to ipratropium.[26] Additionally, a small number of studies suggest that triple therapy (tiotropium + ICS + LABA) is associated with decreased exacerbations compared with ICS+LABA alone or tiotropium alone. [27,28] However, studies comparing tiotropium to LABAs and FSC suggest that there may be a small but significantly increased risk of COPD exacerbations among tiotropium users. [29,30, 31, 32] This evidence is not consistent and many of the studies suffer from the potential of bias to unmeasured confounders..

Network meta-analysis: A network meta-analysis, which included 26 RCTs for a total of 36,312 patients, concluded that combination therapy (in particular roflumilast + LAMA) is likely superior to single therapy regarding exacerbations.[33] A second network meta-analysis that included 35 RCTs with 26,786 patients using inhaled drugs for COPD concluded that no significant differences were noted between LABAs, LAMAs, ICS and ICS+LABA for reducing exacerbations. However, in patients with severe COPD (i.e., FEV1<40% predicted), LAMA , ICSs and ICS+LABA reduced exacerbations significantly compared with LABAs.[34]

Mortality

Observational studies: Studies investigating the risks of mortality among tiotropium users are largely inconsistent. Among three studies comparing tiotropium to LABAs[35, 31, 32], results differed in each of the studies; however the largest study with the longest follow-up suggested that there may be a small elevated risk of mortality among tiotropium users compared to LABA users. [31] Further, a cohort study comparing two different tiotropium devices concluded that Respimat may have an elevated risk of death compared to Handihaler[36]; however, the findings may be biased by selection bias leading to differing population characteristics at baseline. A subsequent RCT that investigated this question found no difference in risk of mortality between these products.[37] Lastly, results from one large study among users of triple therapy suggests that triple therapy may be associated with a reduced risk of mortality

compared to users of ICS+LABA. [28]

Network meta-analysis and meta-analysis: A network meta-analysis examined mortality overall in 42 trials (52,516 patients) of tiotropium *Soft Mist Inhaler*, tiotropium HandiHaler, ICS+LABA, LABA, ICS or placebo.[38] In the fixed effect model, tiotropium Soft Mist Inhaler was associated with an increased risk of overall death compared with placebo (OR 1.51; 95% CI 1.06 to 2.19), tiotropium HandiHaler (OR 1.63; 95% CI 1.10 to 2.44) and ICS+LABA combination (OR 1.90;95% CI 1.28 to 2.86). The risk was greater for cardiovascular death, in patients with severe COPD and at a higher daily dose. ICS+LABA was associated with the lowest risk of overall death. No excess risk was noted for tiotropium Handihaler or LABA.

Lung Function (as measured by FEV1)

A recent Cochrane review and associated network meta-analysis compared four classes of long acting inhalers for COPD (ICS, LABA, ICS+LABA combination, and LAMA) for two efficacy outcomes: mean FEV1 and mean total score on SGRQ.[39]

Compared with placebo, ICS+LABA was the highest ranked class in terms of improved mean FEV1, with a mean improvement over placebo of 133.3 mL (95% credible interval (CrI) 100.6 to 164.0) at 6 months and 100 mL (95% CrI 55.5 to 140.1) at 12 months. LAMAs and LABAs had a similar effect overall (mean difference (MD) 103.5, 95% CrI 81.8 to 124.9; MD 99.4, 95% CRI 72.0 to 127.8, respectively), and ICS ranked fourth (MD 65.4, 95% CrI 33.1 to 96.9).[39] For FEV1, the threshold of clinical significance is 100 to 140mL.[40]

Quality of life (as measured by St. George's Respiratory Questionnaire)

The St. George's Respiratory Questionnaire (SGRQ) is a validated measure of health status in patients with chronic airflow limitation, with scores ranging from zero (perfect health) to 100 (most severe status); the minimal clinically important difference is four units.[39] A Cochrane review and associated NMA showed that similar to lung function, ICS+LABA ranked highest (mean improvement over placebo of -3.89 units, 95% CrI -4.70 to -2.97, at 6 months). LAMAs (MD -2.63, 95% CrI -3.53 to -1.97), LABAs (MD -2.29, 95% CrI -3.18 to -1.53), and ICS (MD -2.00, 95% CrI -3.06 to -0.87) ranked second, third, and fourth, respectively, and all were better than placebo in terms of improved quality of life in patients with COPD. Even though only the ICS+LABA treatment had a mean difference over placebo in line with the minimal clinically important difference of four units, a previous review demonstrated that a treatment that has a mean difference of lower than 4 units on the SGRQ can still lead to a significantly higher number of patients who reach a four-unit change on the SGRQ in the treatment group than the placebo group.[41]

Safety and Tolerability

Pneumonia

Network meta-analysis was conducted for the safety outcome of pneumonia. Thirty-seven RCTs reported on pneumonia and 33 RCTs including 47,628 patients contributed data on 153 treatment comparisons in our network meta-analysis (see Exhibit 5).

No statistically significant differences were observed for any treatment comparisons with LAMA except for:

LAMA vs. ICS+LABA

- Glycopyrronium had a significantly lower risk of pneumonia compared with FVC (NNT 19) and FSC (NNT 21) (Table 5). Similarly, patients who received tiotropium experienced significantly less pneumonia than those receiving FVC (NNT 21) and FSC (NNT 26).

Results of our ranking analysis
The probabilities for being the safest regarding pneumonia were 76% for formoterol, 76% for glycopyrronium, 63% for tiotropium, 62% for MFC, and 58% for indacaterol.

Exhibit 5: Results of meta-analysis and network meta-analysis for pneumonia

Intervention	Comparison	NNH
ICS+LABA vs. LAMA		
Fluticasone + vilanterol	Glycopyrronium	7
Fluticasone + salmeterol	Glycopyrronium	10
Fluticasone + vilanterol	Tiotropium	9
Fluticasone + salmeterol	Tiotropium	14

Note: NNT/NNH calculated using the odds ratio from the meta-analysis whenever network meta-analysis was not statistically significant.

Arrhythmia

Seventeen RCTs including 16,761 patients contributed data on 171 treatment comparisons in a network meta-analysis. For this safety outcome, no statistically significant differences were observed across any of the LAMA or LAMA+LABA comparisons.

Cardiovascular-related mortality

Thirty two RCTs including 76,710 patients contributed data on 190 treatment comparisons in a network meta-analysis. No statistically significant differences were observed for various treatment comparisons or there was no available data for the treatment comparisons except for:

LAMA vs. LABA

- There was a significant increase in risk of cardiovascular-related death for patients treated with tiotropium delivered via Handihaler (NNH 76) or tiotropium delivered via Respimat (NNH 59) when compared with salmeterol.

LAMA vs. ICS+LABA

- There was a significant increase in risk of cardiovascular-related death for patients treated with tiotropium delivered via Handihaler (NNH 131) or tiotropium delivered via Respimat (NNH 94) when compared with FSC.

LABA vs. placebo

- Compared with placebo, there was a significant decrease in risk of cardiovascular-related death for those patients treated with salmeterol alone (NNT 211).

Results of our ranking analysis

The probabilities for being the safest regarding cardiovascular-related mortality were 84% for glycopyrronium, 76% for glycopyrronium+indacaterol, 75% for salmeterol, 69% for AZD3199, and 63% for FSC.

Review of Other Studies

Observational studies: Although an association between inhaled anticholinergic use and acute urinary retention was observed in men (but not women), this risk did not appear to differ between long-acting ((i.e., tiotropium) and short-acting formulations (i.e., ipratropium) of these products. [42,43] A nested case-control study of individuals with COPD was conducted to determine the risk of acute urinary retention with short-acting (namely ipratropium) and long-acting (namely tiotropium) anticholinergics.[42] The authors found that men recently initiating an inhaled anticholinergic had a 42% increased risk of acute urinary retention compared to non-users (odds ratio [OR], 95% CI 1.42, 1.20 to 1.68). No significant finding was observed among women.

There does not appear to be any evidence that use of tiotropium leads to increased risks of cardiovascular disease compared with LABA users. [32, 44]

Pharmacoeconomics Team

Cost-Effectiveness Literature Review

A total of fourteen studies were identified for inclusion for the review (Pharmacoeconomics Team Report). A total of seven were both cost-effectiveness and cost-utility analyses,[45-51] six were cost-utility analyses,[52-57] and one study was a cost-effectiveness analysis.[58]

Only one Canadian study which was a cost effectiveness/utility analysis was identified.[50] Oostenbrink et al.[50] compared LAMA and LABA in patients with moderate-very severe COPD; distinct COPD severity population and age of population modelled were not specified in the analysis. The results from Oostenbrink[50] suggested that LAMA was more cost effective than LABA in terms of incremental cost per exacerbation avoided and incremental cost per quality life adjusted months.

Results from studies funded by manufacturers of LAMA concluded that LAMA was cost effective compared to LABA or dominated LABA,[45;46;48-50;52;56;57] while results from studies sponsored by manufacturers of LABA reported that LABA was cost effective compared to LAMA or dominated LAMA.[51;55;56]

Overall, the studies identified in this review are of limited applicability to the current Canadian setting. Studies identified in the systematic review of economic evidence have contradictory results and the quality and relevance of these studies limit their applicability to this study's questions.

De novo Economic Evaluation

An economic model developed for the LABA+ICS class review was used to assess the cost effectiveness of alternative reimbursement strategies for LAMA monotherapies and LAMA+LABA combination therapies. A Markov model was developed which modelled disease progression over a lifetime time horizon combined with rates of exacerbations and death. Natural history data relating to disease progression was combined with treatment effectiveness (i.e., exacerbations) and adverse event data from the clinical review conducted as part of this class review. Costs and utilities associated with disease severity, treatment related adverse events and exacerbations were derived from the literature and from our rapid review. Analysis was conducted from the perspective of the payer (Ministry of Health) with results presented as incremental cost per quality adjusted life years gained. Detailed deterministic and probabilistic sensitivity analysis was performed to determine decision uncertainty.

- Based on current list prices, the de novo economic evaluation did not find LAMA monotherapies cost effective when compared to formoterol (Oxeze) (LABA). Tudorza (LAMA) was cost effective compared to other LAMAs (i.e., Seebri and Spiriva), although there is a great deal of uncertainty over this finding.
- Based on current listing prices, the de novo economic evaluation did not find LAMA/LABA combination therapies cost effective when compared to budesonide/formoterol (Symbicort) (ICS/LABA). Note that any uncertainty in our NMA would affect the results of the pharmacoeconomic analyses. When considering only the LAMA/LABA combination therapies, indacaterol/glycopyrronium (Ultibro) is dominant over umeclidinium/vilanterol (Anoro Ellipta) – i.e., less costly and more effective. Triple therapy with tiotropium/fluticasone/salmeterol (Spiriva plus Advair Diskus) is not cost effective compared to ICS/LABA combination therapies.

Budget Impact Analysis

In 2012, total expenditure by OPDP on COPD therapy (including all long-acting bronchodilators i.e., LABA, LAMA, ICS and ICS+LABA) for patients with at least moderate COPD was $149.1 million. LAMAs comprised 34% of this drug expenditure ($50.1 million). Total costs for LAMAs ranged from $8.5 million for patients with severe COPD to $30.1 million for patients with moderate COPD.

All LAMA products are currently available as General Benefit on the ODB formulary; it is assumed that listing of additional LAMA products will not have a major budget impact. However, for the LAMA+LABA combination products, it is assumed that a general benefit listing for these products would lead to an increase in total expenditure on COPD therapy of 17% (see Exhibit 6). Negotiating a 25% price reduction with both LAMA+LABA products would lead to an increase in expenditure of $7.8 million (or 5.2%). In a sensitivity analysis whereby the use of LAMA+LABA products was assumed to be similar to previous use of LAMA products and half the users of LABA+ICS products were switched to a LAMA+LABA, the increase in budget was minimal ($838,000 or 0.56%).

Reimbursement-Based Economic Assessment

Assuming that use of LAMA products is not expected to increase and that there is a willingness to continue to reimburse LAMA therapies, an optimal policy, assuming a willingness to pay of $50,000 per QALY, would be to list only Tudorza at currently listed prices. If price reductions for the other LAMAs could be negotiated this conclusion may change.

Assuming a willingness to pay of $50,000 per QALY, it is not cost effective to fund either LAMA/LABA combination products if there is an inability to negotiate a price reduction. If decision makers can negotiate a price reduction of at least 29%, reimbursement of Ultibro for patients with at least moderate COPD would be optimal.

Exhibit 6: Budget impact (for at least moderate COPD severity)

Scenario	Impact	Base Case		Reduced Price*	
		Total	% Budget Impact	Total	% Budget Impact
Current Expenditure**		**$149,096,674**			
Expenditure with reimbursement of LAMA+LABA combination therapies	Expected total $	$174,455,344	**17.008%**	$156,870,711	**5.214%**
	Budget impact	+ $25,358,670		+ $7,774,037	

*25% price reduction from current list price for both LAMA+LABA products (Anoro Ellipta and Ultibro)
**Total COPD expenditures by OPDP from April 1, 2012-March 31, 2013: includes ICS, LABA, LAMA and ICS+LABA therapies

Summary

Review of Economic Literature: Studies identified in the systematic review of economic evidence have contradictory results and the quality and relevance of these studies limit their applicability to this study's questions.

De novo Economic Evaluation: The de novo economic evaluation found that LAMA monotherapies were cost effective when compared to ICS single agents and Serevent, but not to formoterol (Oxeze) at the listed drug prices. As well, the analysis did not find LAMA+LABA combination therapies cost-effective when compared to Symbicort. Triple therapy (i.e., LAMA plus ICS+LABA) was not cost-effective compared to ICS+LABA combination therapies.

Budget Impact Analysis: Assuming a general benefit listing for LAMA+LABA combination products, an increase in total expenditure on COPD therapy would be anticipated ranging from 0.14-17%, depending on the clinical use of these new agents. A sensitivity analysis whereby the number of units of LAMA+LABA products was based on previous use of LAMA and ICS+LABA products forecasted a smaller

budget increase of less than 1%.

Negotiating a 25% price reduction with both LAMA+LABA products may lead to a reduction in expenditures ($2.5 million or 1.7%) or, depending on the scenario for use of these new agents, to an increase in expenditures ($7.8 million or 5.2%).

Reimbursement based Economic Assessment: Assuming a willingness to pay of $50,000 per QALY, it may not be cost effective to fund either LAMA+LABA combination product (Ultibro or Anoro Ellipta) if there is an inability to negotiate a price reduction. However, if a price reduction of at least 29% relative to its currently listed price can be negotiated, reimbursement of Ultibro for patients with at least moderate disease would be optimal.

Health Equity Issues

No major health equity issues were identified in this review. See Appendix A for Health Equity Considerations.

Accessibility of LAMA products

LAMAs are available as a general benefit in Ontario, for qualifying patients. As such, no accessibility issues were identified in our review. For patients under the age of 65 and without public or private coverage, access to COPD medications including LAMAs may be a challenge as LAMAs cost approximately $60/month.

Use in elderly

Overall, the majority of treated COPD patients using LAMAs were over 65 years of age; this is likely driven by the prevalence of COPD and ODB eligibility criteria. Our analysis found that COPD patients prescribed LAMAs tended to be over 65 years of age, have moderate COPD severity, and live in urban locations.

Use in Women

In Ontario, there are 850,000 people (11.8% of the population) diagnosed with COPD, with females comprising 50.6% of the COPD population.[5] This is also reflected in the Ontario data, where analysis showed that use of LAMAs was comparable among males (49.8%) and females (50.2%).

Reimbursement Options for Consideration

Key Considerations

Efficacy

- For exacerbations in patients with moderate COPD, LAMA products were found to be more effective than LABAs. However, individual LAMAs products were found to be inferior to ICS+LABA products.
- When LAMA products were compared, no statistically significant differences were observed.
- In our NMA, for the comparison of LAMAs vs LAMA+ICS+LABA ("triple therapy"), there was insufficient data to draw meaningful conclusions. Although no statistically significant

differences were observed for LAMAs vs LAMA+ICS+LABA ("triple therapy") with respect to exacerbations, this finding may be due to a lack of evidence to detect a true difference between the agents; only two trials including 756 patients provided direct evidence on this treatment comparison.

- LAMA+LABAs decreased the risk of exacerbation compared with LABAs. However, no statistically significant difference was noted with LAMA+LABAs for exacerbations in patients with moderate COPD in comparison to individual LAMAs, ICS+LABAs or LAMA+ICS+LABAs. Note that for the LAMA+LABA versus ICS+LABA and LAMA+LABA versus LAMA+ICS+LABA results, there was insufficient data to draw meaningful conclusions as only one trial provided direct evidence on each of these treatment comparisons.

Safety and tolerability

- For the safety outcome of arrhythmias, no statistically significant differences were observed across any of the LAMA or LAMA+LABA comparisons.
- In contrast, LAMAs had a lower risk of pneumonia relative to ICS+LABA.

Accessibility

- LAMAs are available as a general benefit in Ontario, for qualifying patients, including those 65 years and older. As such, no accessibility issues were identified in our review.
- For patients under the age of 65 and without public or private coverage, access to COPD medications including LAMAs may be a challenge as LAMAs cost approximately $60/month.

Pharmacoeconomics

- *De novo Economic Evaluation:* The de novo economic evaluation found that LAMA monotherapies were cost effective when compared to ICS single agents and Serevent, but not to formoterol (Oxeze) at the listed drug prices. As well, the analysis did not find LAMA+LABA combination therapies cost-effective when compared to Symbicort. Triple therapy (i.e., LAMA plus ICS+LABA) was not cost-effective compared to ICS+LABA combination therapies.
- *Budget Impact Analysis:* If LAMA+LABA combination products are listed as a general benefit at currently listed prices, an increase in total expenditure on COPD therapy would be expected at 17%. Negotiating a 25% price reduction with both LAMA+LABA products would lead to an increase in expenditures ($7.8 million or 5.2%).
- *Reimbursement based Economic Assessment:* Assuming a willingness to pay of $50,000 per QALY, it may not be cost effective to fund either LAMA+LABA combination product (Ultibro or Anoro Ellipta) if there is an inability to negotiate a price reduction. However, if a price reduction of at least 29% relative to its currently listed price can be negotiated, reimbursement of Ultibro for patients with at least moderate disease would be optimal.

Reimbursement Options

Reimbursement options for LAMAs for COPD as well as ICS+LABA for COPD and asthma will be presented at the completion of the drug class review for ICS+LABA for asthma.

Conclusion

Final recommendations for the funding of LAMAs for COPD through the publicly funded drug program in Ontario will be made upon completion of the Social Acceptability Research (led by the Qualitative Research Team) and the Stakeholder Review that will be conducted as part of the review of ICS+LABA for asthma drug class review.

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Appendix A: Health Equity Considerations for LAMA for COPD Drug Class Review

Populations Identify which populations may experience significant unintended health impacts (positive or negative) as a result of the planned policy, program or initiative.	Comments: Proposed LAMA Coverage
Aboriginal peoples (e.g., First Nations, Inuit, Métis, etc.)	No accessibility issues identified. Coverage of medications, including ICS+LABA, for aboriginal peoples is available through Ontario Ministry of Health and Long-term Care.
Age-related groups (e.g., children, youth, seniors, etc.)	Children/youth: COPD is considered a disease of adulthood. No recommendations for listing made for children and adolescents in the review. Elderly: No restrictions for LAMA use in the elderly were identified in the review.
Disability (e.g., physical, D/deaf, deafened or hard of hearing, visual, intellectual/developmental, learning, mental illness, addictions/substance use, etc.)	No accessibility issues identified. Patients with disability and receiving Ontario Disability Support Program Income Support, receive prescription drug coverage (including LAMAs) through ODB.
Ethno-racial communities (e.g., racial/racialized or cultural minorities, immigrants and refugees, etc.)	No accessibility issues identified.
Francophone (including new immigrant francophones, deaf communities using LSQ/LSF, etc.)	No accessibility issued identified.
Homeless (including marginally or under-housed, etc.)	Not eligible for ODB coverage.
Linguistic communities (e.g., uncomfortable using English or French, literacy affects communication, etc.).	No accessibility issues identified.
Low income (e.g., unemployed, underemployed, etc.)	No accessibility issues identified; low income individuals who receive public drug coverage will have access to LAMAs through ODB.
Religious/faith communities	No accessibility issues identified.
Rural/remote or inner-urban populations (e.g., geographic or social isolation, under-serviced areas, etc.)	No accessibility issues identified.
Sex/gender (e.g., male, female, women, men, trans, transsexual, transgendered, two-spirited, etc.)	No accessibility issues identified for sex/gender in the review.
Sexual orientation, (e.g.,lesbian, gay, bisexual, etc.)	No accessibility issues identified.
Other: please describe the population here.	None identified.

(based on Health Equity Impact Assessment http://www.health.gov.on.ca/en/pro/programs/heia/)