Inhaled Corticosteroids (ICS) + Long-Acting Beta-Agonists (LABA) for the Treatment of Chronic Obstructive Pulmonary Disease (COPD)

Final Consoildated 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 ICS+LABA for COPD Drug Class Review.

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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 Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).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
CED	Committee to Evaluate Drugs
CDEC	Canadian Drug Expert Committee
CHMS	Canadian Health Measures Survey
CIHI	Canadian Institute for Health Information
COPD	Chronic obstructive pulmonary disease
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 antagonists
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
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 four inhaled corticosteroid and long-acting beta-agonist (ICS+LABA) combination products available: fluticasone + salmeterol (FSC), budesonide + formoterol (BFC), fluticasone + vilanterol (FVC), and mometasone + formoterol (MFC). Three ICS+LABA products (i.e., FSC, BFC, MFC) are available in Ontario on the Ontario Drug Benefit formulary only for the treatment of asthma under the Limited Use program. As part of the formulary modernization review, an evaluation of ICS+LABA combination products for the management of patients with chronic obstructive pulmonary disease (COPD) was undertaken to provide recommendations for funding of these products in Ontario for COPD. Detailed information for each of the reports can be found on the ODPRN website. Long-acting muscarinic agents (LAMAs) for COPD and ICS+LABA for asthma will be reviewed by ODPRN as separate drug class reviews (both launched in spring 2014). Due to overlapping themes, final policy recommendations for all three drug classes will be released upon completion of the three reviews.

Key Considerations for Reimbursement Options

Efficacy and Safety

As a class, ICS+LABA combination products have been shown to reduce exacerbation rates and improve lung function and quality of life in patients with COPD relative to other available therapies. Overall, for the outcome of any exacerbations for moderate COPD, our network meta-analysis showed that ICS+LABA combination products were more effective than other long-acting inhaled therapies for COPD, including LABAs, long-acting muscarinic antagonists (LAMAs) and ICS products.

The balance between the risks and benefits of ICS+LABA combination products must be carefully considered. An increased risk of pneumonia has been attributed to ICS, either alone or in combination with LABA, relative to any comparator. Our analyses indicate that fluticasone, alone or in combination with a LABA, is associated with a greater risk of pneumonia relative to placebo, budesonide (alone or in combination with a LABA) or a LABA. For the safety outcome of arrhythmias, no statistically significant differences were observed across any of the ICS+LABA agents compared with each other, ICS alone, LABA alone, or placebo. It should be noted that no head-to-head randomized controlled trials have been done comparing BFC and FSC for efficacy or safety; there are some observational studies although the results are not consistent.

Accessibility

Despite the lack of public drug coverage of ICS+LABA products for COPD in Ontario, no accessibility issues were identified in our review. In our one-on-one interviews with respirologists and primary care physicians it was noted that physicians often resort to using the Limited Use (LU) code 330 for asthma to access these drugs for their patients who are eligible for drug coverage. For patients under the age of 65 and without public or private coverage, access to COPD medications including ICS+LABA may be a challenge as some patients are unable to afford these medications.

Utilization

ICS+LABA combination products are the second-most commonly prescribed inhaled respiratory medications for all indications in Canada, with 1.1 million prescriptions dispensed in the fourth quarter of 2013; short-acting beta-agonists (e.g., salbutamol) are the most frequently prescribed inhaled respiratory medications in Canada with 1.8 million prescriptions dispensed in the same time period. Approximately 63% of all patients eligible for public drug coverage in Ontario who were prescribed an ICS+LABA combination product had a diagnosis of COPD (either with or without a concurrent diagnosis of asthma). Although Ontario currently only funds ICS+LABA for the indication of asthma, approximately 47% of users did not have any indication of asthma (28% COPD diagnosis only, 20% no evidence of asthma or COPD).

Pharmacoeconomics

In patients receiving ICS and LABA via separate inhalers, our de novo economic evaluation supports the cost effectiveness of moving to administration of the combination via a single inhaler. Since the cost of ICS+LABA combination therapy is less expensive than ICS and LABA dual therapy and as many patients with COPD are already receiving ICS+LABA combination therapy using the LU code for asthma, there is minimum expected impact on COPD total drug costs if Advair and/or Symbicort are moved to Limited Use.

The incremental cost per QALY gained for ICS+LABA combination when compared with LABA alone ranged from $80,000 to $260,000 depending on the severity of disease. The incremental cost per QALY gained for triple therapy with ICS+LABA combination in addition to LAMA compared with LAMA alone ranged from $85,000 to $160,000 depending on the severity of disease.

Reimbursement Options

Reimbursement options for ICS+LABA for COPD will be reviewed at the completion of the drug class reviews for LAMA for COPD and ICS+LABA for asthma.

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Rationale for Review

In Canada, there are four available ICS+LABA combination products (referred to in the rest of this document as "ICS+LABA"). Two of these, namely fluticasone + salmeterol combination (FSC) (Advair Diskus) and budesonide + formoterol combination (BFC) (Symbicort), are indicated for both COPD and asthma. Fluticasone + vilanterol combination (FVC) (Breo Ellipta) is only indicated for the treatment of COPD. Mometasone + formoterol combination (MFC) (Zenhale) and FSC available as a metered dose inhaler (Advair) are currently licensed in Canada for the treatment of asthma only.

In Ontario, three ICS+LABA products (i.e., FSC, BFC, MFC) are available on the ODB formulary only for the treatment of asthma under the Limited Use program. However, in all other public drug programs across Canada, at least one of the ICS+LABA products is funded for the management of patients with COPD. Ontario's Committee to Evaluate Drugs (CED) reviewed the available evidence in 2003 and 2004 for use of Advair Diskus in patients with COPD. At that time, the CED concluded that there was insufficient evidence to demonstrate additional clinical benefit or value for money compared with standard available therapy. The manufacturer of Symbicort did not submit a request for review of this product for COPD. Since the last review of Advair by the CED, there have been landmark trials that have provided new evidence about the role of ICS+LABA in the management of patients with COPD.[1-3]

As part of the formulary modernization review, an evaluation of ICS+LABA combination products for the management of patients with COPD was undertaken to provide recommendations for funding 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

Chronic obstructive pulmonary disease (COPD) is a common and debilitating lung disease that is characterized by progressive airflow obstruction (partially reversible), inflammation in the airways and systemic effects.[4] COPD is presently the fourth leading cause of death, but WHO predicts that by 2030 it will become the third leading cause of death worldwide.[5] 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.[4;6]

The worldwide prevalence of COPD is more than 10% among adults aged 40 years and older.[7] In Ontario, there are 850,000 people age 35 and older (11.8% of the population) diagnosed with COPD.[8] In a study using Ontario data, the prevalence of COPD increased by 64.8% between 1996 and 2007 (76% in women and 55% in men, $p<0.001$).[9] 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.[10] Canadian data indicate 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.[11] 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%. As well, although asthma and COPD are different respiratory diseases, asthma and COPD may coexist. [8;12;13]

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.[14] 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).[15] 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.[8] 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).[16]

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).[17] 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.[18] Drug therapy includes use of a bronchodilator to control symptoms with use of inhaled corticosteroid (ICS) in patients with more severe disease.[4] 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.[18]

In Canada, there are four ICS+LABA combination products available. Two of these, namely fluticasone + salmeterol combination (FSC) (Advair Diskus) and budesonide + formoterol combination (BFC) (Symbicort), are indicated for both COPD and asthma. Fluticasone + vilanterol combination (FVC) (Breo Ellipta) is only indicated for the treatment of COPD. Mometasone + formoterol combination (MFC) (Zenhale) and FSC available as a metered dose inhaler (Advair) are currently licensed in Canada for the treatment of asthma only. Symbicort, BreoEllipta and Advair Diskus are available as a dry powder inhaler (DPI). Advair and Zenhale are available as a hydrofluoroalkane-propelled metered dose inhaler (MDI). There are currently no generic products available in Canada.

Public plan reimbursement of ICS+LABA combination products in Canada

In Ontario, four ICS+LABA products (i.e., Advair Diskus, Advair, Zenhale, Symbicort) are available on the ODB formulary only for the treatment of asthma under the Limited Use program. However, in all other public drug programs across Canada, at least one of the ICS+LABA products is funded for the management of patients with COPD (Environmental Scan Report). Nine of the 12 (75%) public drug programs in Canada list ICS+LABA on a restricted basis (i.e., requiring prior authorization) for the treatment of COPD (for details on coverage, see Exhibit 1). In two provinces (Alberta and Manitoba),

Advair and Symbicort are listed as general benefits. Restriction criteria vary among the public drug plans and include use of spirometry for confirmation of diagnosis in five plans, prior use of SABA and/or SAMA in four plans, and prior use of LAMA and/or LABA in two plans.

Zenhale was reviewed by the Common Drug Review (CDR) in September 2012 for the indication of asthma only; a recommendation was made to list this product similar to other combination ICS+LABAs for asthma maintenance. The CDR reviewed Breo Ellipta in August 2014; it was recommended that this product be listed with criteria for patients with chronic obstructive pulmonary disease.

Exhibit 1: Public plan listings in Canada for ICS+LABA combination products

	Advair		Symbicort		Zenhale	BreoEllipta*
	Asthma	COPD	Asthma	COPD	Asthma	COPD
BC	Res	Res	Res	No	Res	No
Alberta	Ben	Ben	Ben	Ben	No	No
Saskatchewan	Res	Res	Res	Res	Res	No
Manitoba	Ben	Ben	Ben	Ben	No	No
Ontario	Pas	No	Pas	No	Pas	No
Quebec	Res	Res	Res	Res	Res	No
New Brunswick	Res	Res	Res	Res	Res	No
Nova Scotia	Res	Res	Res	Res	Res	No
PEI	Res	Res	Res	Res	Res	No
Newfoundland	Res	Res	Res	Res	Res	No
Yukon	Res	Res	Res	Res	No	No
NIHB/NT/NU	Res	Res	Res	Res	Res	No

*Breo Ellipta received its Notice of Compliance in July 2013 and final CDEC recommendations were posted in August 2014.
No=not listed; Res=restricted listing – enforced; Pas= restricted listing – passive; Ben=unrestricted listing

Objective

The objective of the ICS+LABA for COPD drug class review is to provide evidence-informed recommendations for the funding of ICS+LABA for COPD through the publicly funded drug program in Ontario. Long-acting muscarinic agents (LAMAs) for COPD and ICS+LABA for asthma will be 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 reviews.

Components of the Drug Class Review

The comprehensive approach to ICS+LABA for COPD drug class review is comprised of:

- qualitative analyses of perspectives of patients, pharmacists and prescribers
    - one-on-one semi-structured telephone interviews regarding specific experiences and perceptions relevant to funding policies for ICS+LABA 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 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.

Our results are similar to published reports. Patients with COPD have a high symptom burden;[19] in particular, patients with advanced COPD have symptoms that are comparable to those patients with cancer or congestive heart failure.[20] In addition, COPD has a major impact on healthcare costs, lost productivity, absenteeism and presenteeism in the workplace.[21;22]

> *"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 a, always on the back of my mind, how is this going to affect my breathing." - Patient*

Challenges in treating COPD

Participants in the qualitative study noted that COPD therapies such as ICS+LABA are perceived to be useful for preventing exacerbations, but there were disparate perceptions on the effect of ICS+LABA on quality of life. 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.

Clinician participants, including respirologists and primary care physicians, felt that these maintenance drugs should be reserved only for severe patients, despite the guidelines, including the Canadian Thoracic Society, indicating that they can be used in patients with moderate to severe disease severity .[18;23-25] However, there are challenges with the over and under diagnosis of COPD that can affect both appropriateness of treatment and access to the appropriate medications. Some physician participants admitted having difficulty remembering the correct diagnostic criteria for patients who present with respiratory symptoms and with interpreting spirometry results. In some cases primary care physicians described experiences of incorrectly diagnosing patients with COPD and prescribing them combination ICS+LABA products that were not necessary for their condition.

Physician participants also highlighted factors that affect the selection of appropriate treatments for specific COPD patients, including: varied responsiveness to ICS+LABA depending on COPD phenotypes (e.g., asthma and bronchitis phenotypes), which may therefore impact a physician's decision to prescribe ICS+LABA; and a "steroid philosophy", where differences in opinions between physicians on the use of steroids can affect when steroid therapy is introduced to patient treatment regimens.

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 LAMAs.

> *"It's pretty hard to separate that out from the effectiveness of Spiriva in doing the same because I use them both [ICS+LABA and LAMA]. I, again, don't have enough patients to be able to tell you, like, "This population has just been on Spiriva and this has been on both," and compare their rates of exacerbation, because it's usually confounded by other things like their lifestyle and, you know, just their health access or health-seeking behaviour in general." - Physician*

Accessibility of ICS+LABA Combination Products for COPD

ICS+LABA is frequently prescribed to ODB-eligible COPD patients even though these drugs are not listed on the formulary for COPD indications. Physicians often resort to using the Limited Use (LU) code 330 for asthma to access these drugs for their ODB- eligible patients (which comprise the majority of their COPD patients). Although physician participants understood the purpose of the code, they described feeling left with no options for COPD patients over 65 years of age who do not have adequate drug coverage. Physician participants perceived that there would be great access issues for many of their patients if

they were not willing to use the LU code 330. Patients under 65 years of age who do not have public or private coverage are at a great disadvantage and are often unable to afford COPD therapies.

Overall, participants from both clinician and patient groups stated that the DPI products are easier to use than the metered dose inhalers. However, ease of use of any of the inhaler products was reported by all participant groups to be enhanced by education, either in pharmacy, clinic or at pulmonary rehabilitation. It should be noted that studies have shown that when used correctly, there is little difference in clinical efficacy between different inhaler devices.[26] One factor to consider in the choice of an inhaler is patient preference.[26] Increased satisfaction with a particular device may lead to increased adherence and subsequent better clinical outcomes.[27]

Both physicians and pharmacists have reservations about the appropriateness of using ICS+LABA combination products before other drugs such as LAMAs in patients early in their COPD diagnosis.

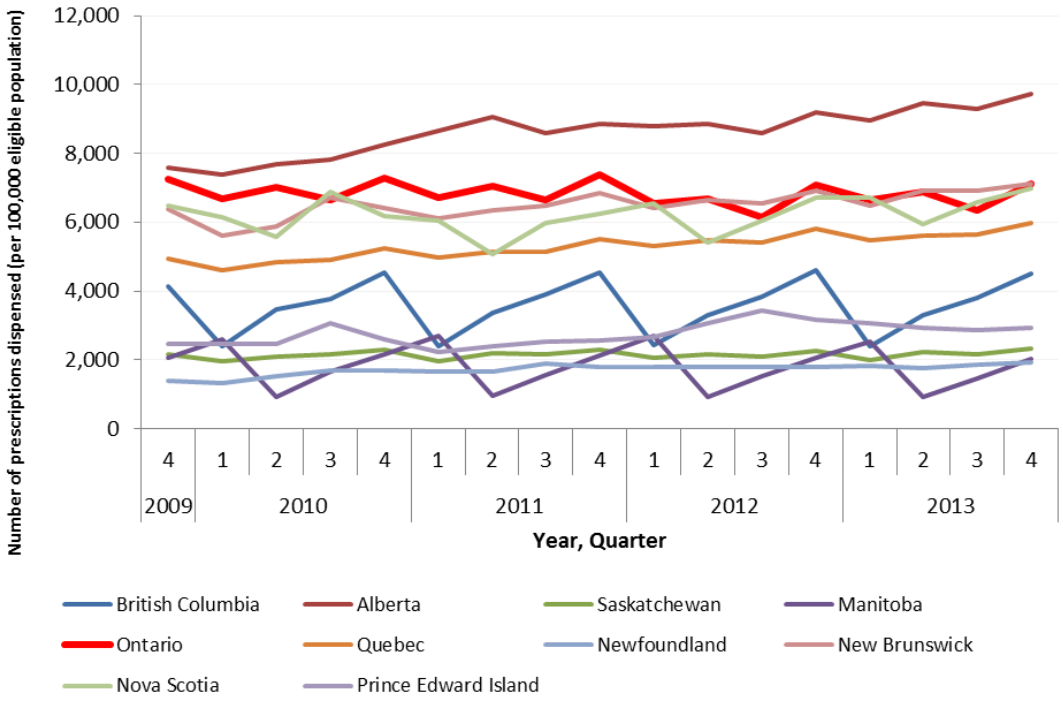
> *"What worries me is when I see someone an Advair or Symbicort and then a, you know, a short-acting Ventolin along with it, and I suspect they might have COPD but I don't know and I feel like, "Jeez, have you tried the anti-cholinergic? Why don't we have an anti-cholinergic on board?" That's the one that leaves me... if they're on the tiotropium and we're now adding an ICS/LABA combination I feel better, but if I suspect, "Jeez, I wonder if this guy has COPD?" or a lady has COPD, then I worry if I don't see the anti-cholinergic."- Pharmacist*

Pharmacoepidemiology Team

Current Utilization in Canada and Ontario

ICS+LABA products are the second-most commonly prescribed inhaled respiratory medications (for all indications) in Canada, with 1.1 million prescriptions dispensed in the fourth quarter (Q4; October to December) of 2013 (see Exhibit 2). Over half (56.5%; Q4 2013) of all prescriptions for ICS+LABA dispensed in Canada were for Advair (Diskus and MDI). Breo Ellipta (FVC) was only commercially available in Canada in November 2013, and therefore data for this product is not available. Ontario has the second-highest utilization rate of provincially funded ICS+LABA (7,127 prescriptions dispensed per 100,000 eligible population vs. national average of 5,063 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. Just over half of all ICS+LABA dispensed in Ontario (regardless of indication) are paid for through the Ontario Public Drug Program (OPDP) (Pharmacoepidemiology Team Report).

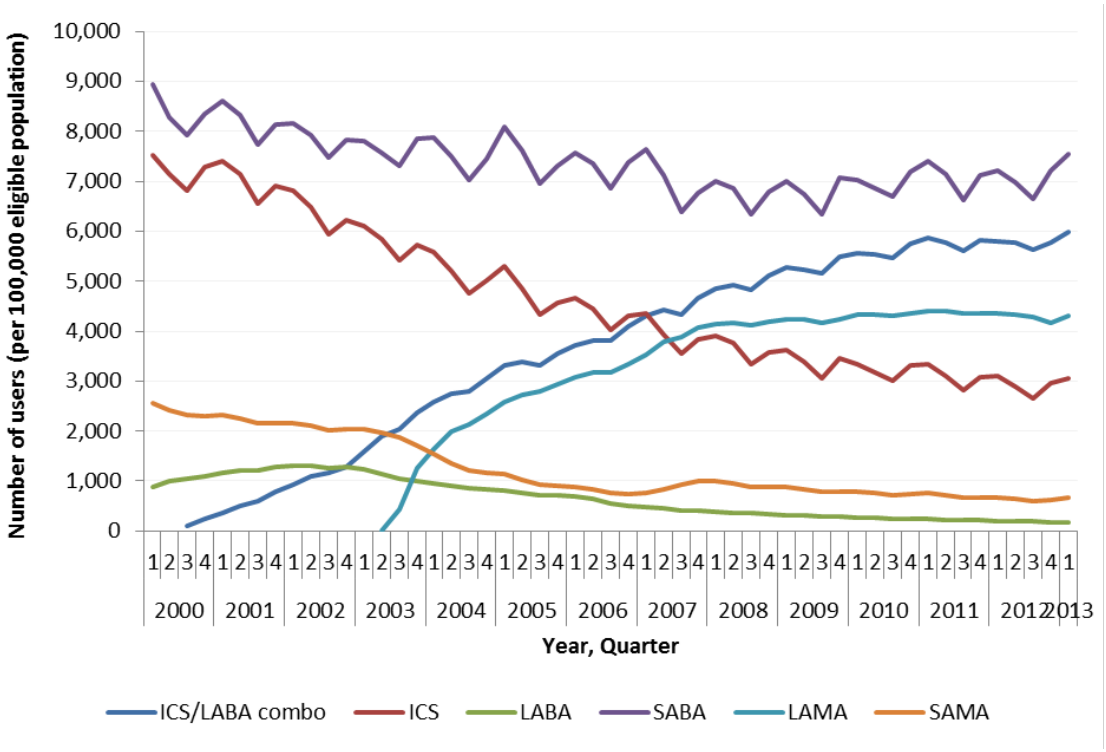
Exhibit 2: Population-adjusted (per 100,000 eligible population) utilization of provincially funded ICS+LABA combination products in Canada, by province



Use of ICS+LABA has been increasing over time (regardless of indication). The rate of use of ICS+LABA in Ontario increased to 5,993 per 100,000 beneficiaries between the introduction of these products in 2000 and the first quarter of 2013 (see Exhibit 3). Over this same time, there has been a corresponding decline in utilization of single-agent ICS and LABA products.

In fiscal year 2012, 62.6% of all patients eligible for public drug coverage in Ontario who were prescribed ICS+LABA had a diagnosis of COPD (either with or without a concurrent diagnosis of asthma). Among the 120,990 COPD patients who received provincially-funded ICS+LABA, almost one-quarter (29,151; 24.1%) were new users. In general, COPD patients prescribed ICS+LABA through the public drug program in Ontario tended to be over 65 years of age, have moderate COPD severity, and live in urban locations. The majority of COPD patients who were treated with both ICS and LABA used ICS+LABA combination products; only 2% (N=1,308) were treated concurrently with single-agent ICS and LABA products ("dual therapy").

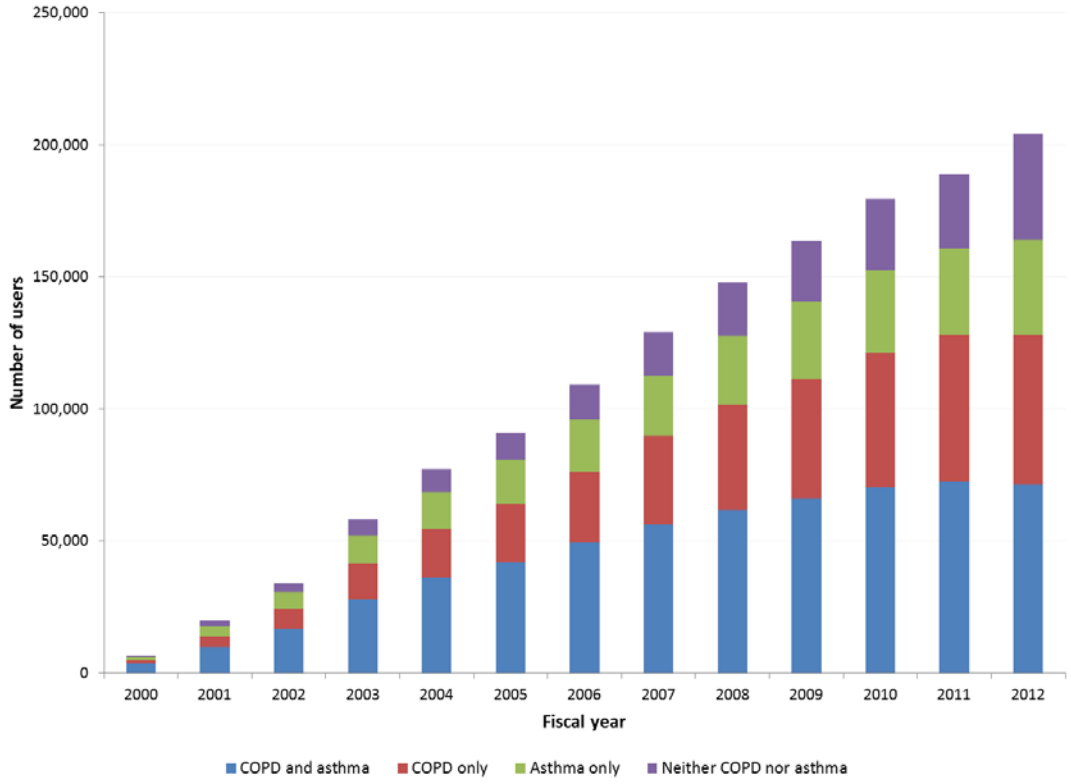
Exhibit 3: Rate of use of inhaled respiratory therapies among public drug plan beneficiaries in Ontario for all indications



Use of ICS/LABA Combination Products for Non-asthma, Non-COPD Indications

BFC (Symbicort) and FSC (Advair, Advair Diskus) are indicated in Canada for the management of patients with asthma and/or COPD.[28;29] However, the Ontario public drug formulary only provides coverage for these medications for the treatment of asthma. Additionally, Ontario provides coverage for MFC (Zenhale) for patients with asthma. Breo Ellipta is currently not funded in Ontario. Results from our analysis indicate that 47.4% of all users of ICS+LABA (2012) did not have any indication of asthma using validated databases at ICES (27.7% COPD diagnosis only, 19.7% no evidence of asthma or COPD) (see Exhibit 4). Of the users with no evidence of asthma or COPD, 7.4% had a history of a prior respiratory disease. Although these results may be due in part to our inability to capture some COPD and asthma cases (e.g. mild cases), it also suggests that these products may be used for off-label indications. Possible off-label uses for ICS+LABA combination products include post-viral cough; however, there is limited published peer-reviewed literature to support the use of ICS+LABA for non-asthma or non-COPD indications.

Exhibit 4: Number of users in Ontario of provincially-funded ICS+LABA combination products, by indication



Adherence

In our analysis, there were no major differences in adherence between users of BFC and FSC (p=0.55); however, analyses adjusted for important confounders (such as history of asthma and COPD severity) found a small but significant difference in adherence between the three listed ICS+LABA products in Ontario with Advair users least likely and Zenhale users most likely to discontinue therapy; this result should be interpreted with caution. It should be noted that Zenhale was only recently added to the formulary and there have been small number of patients treated with this product. Furthermore new users of Zenhale may have failed Advair and/or Symbicort previously, and therefore this finding could be influenced by channeling bias.

Although pharmacotherapy is effective in controlling symptoms and maintaining lung function, research has suggested that half of COPD patients fail to use any maintenance medications.[30] Two cohort studies reported comparative adherence to ICS+LABA therapy as secondary analyses. [31] [32] These studies found no major differences in adherence between BFC and FSC (as defined using medication possession ratios).

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)] (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 done for all severity of COPD disease but inconsistency was present statistically; therefore, the sub-network meta-analysis for exacerbations for patients with moderate COPD was completed. This comprised of 68 RCTs that included 53,412 people (see Exhibit 5).

Exacerbations for moderate COPD

ICS+LABA combination products vs. placebo

- Compared with placebo, there was a significant decrease in risk of COPD exacerbation for those patients with moderate COPD treated with BFC (number needed to treat: NNT 6), FSC (NNT 17), and MFC (NNT 7).

ICS+LABA vs. ICS+LABA

- A statistically significant difference was observed for BFC (NNT 10) and MFC (NNT 8) compared with FSC for decreasing the risk of exacerbation in patients with moderate COPD.
- No statistically significant difference in exacerbations between BFC and MFC was found for patients with moderate COPD.
- According to our ranking analysis, the two ICS+LABA agents with the highest probability of being the most effective for decreasing risk of COPD exacerbation in patients with moderate COPD were BFC and MFC. Note that MFC is not officially indicated for the management of patients with COPD.

ICS+LABA vs. other treatments for COPD

- BFC and MFC decreased the risk of exacerbation when compared with budesonide (NNT 6), indacaterol (NNT 7) and salmeterol (NNT 8). When compared with vilanterol, treatment with BFC (NNT 7), FVC (NNT 16), or MFC (NNT 8) led to decreased risk of exacerbation. Comparison with LAMAs will be reported in the upcoming LAMA drug class review.

Exhibit 5: Results of network meta-analysis for risk of exacerbation with moderate COPD*

Intervention	Comparison	NNT
ICS+LABA vs. placebo		
Budesonide + formoterol	Placebo	6
Fluticasone + salmeterol	Placebo	17
Mometasone + formoterol	Placebo	7
ICS+LABA vs ICS+LABA		
Mometasone+ formoterol	Fluticasone + salmeterol	10
Budesonide + formoterol	Fluticasone + salmeterol	8
ICS+LABA vs. ICS alone or LABA alone		
Budesonide + formoterol	Budesonide	6
Mometasone + formoterol	Budesonide	6
Budesonide + formoterol	Indacaterol	7
Mometasone + formoterol	Indacaterol	7
Budesonide + formoterol	Salmeterol	8
Mometasone + formoterol	Salmeterol	8
Budesonide + formoterol	Vilanterol	7
Fluticasone + vilanterol	Vilanterol	16
Mometasone + formoterol	Vilanterol	8

*only statistically significant results are presented

Review of Observational Studies for Exacerbation

Four population-based cohort studies compared rates of COPD exacerbations between users of BFC and FSC. The findings, however, from these studies are not consistent. This may be driven by the differential follow-up in each study. Two studies conducted in the United States by the same group of authors found no overall difference in COPD exacerbations between the two exposure groups, although follow-up was limited to 6 months.[32;33] In contrast, two additional studies compared ICS+LABA in Sweden and Canada. The Swedish study, with a follow-up of 3.5 years, found that individuals treated with BFC had fewer COPD exacerbations than those treated with FSC. The Canadian study, with a follow-up of 1 year, concluded that those initiating BFC were significantly less likely to have emergency department (ED) visits or hospitalizations for COPD relative to those initiating FSC.[31;34] However, the results from Canadian study must be interpreted with care, as the matching did not appear to create treatment groups that were comparable at baseline, and therefore unmeasured confounding may have influenced these findings.[31]

Review of Other Outcome Measures

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 St. George's Respiratory Questionnaire (SGRQ).[35]

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).[35] For FEV1, the threshold of clinical significance is 100 to 140mL.[36]

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

The St. George's Respiratory Questionnaire (SGRQ) is a well-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.[35] The 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.

Safety and tolerability

Pneumonia

An increased risk of pneumonia has been attributed to ICS, either alone or in combination with LABA. A network meta-analysis was conducted by the rapid review team for the safety outcome of pneumonia. A total of 33 RCTs including 47,628 patients contributed data on 153 treatment comparisons in the network meta-analysis (see Exhibit 6).

ICS+LABA vs. placebo

- Statistically significantly more patients receiving FVC (number needed to harm: NNH 10) and FSC (NNH 16) experienced pneumonia versus patients who received the placebo.

ICS+LABA vs. ICS+LABA

- Significantly more patients taking FSC experienced pneumonia versus BFC (NNH 19).
- In terms of ranking, the probabilities for being the safest (for pneumonia) for ICS+LABA were 62% for MFC, 56% for BFC, 14% for FSC, and 10% for FVC, according to the surface under the cumulative ranking curve (SUCRA).

ICS+LABA vs. ICS alone or LABA alone

- Statistically significantly more patients taking FVC experienced pneumonia compared with budesonide (NNH 9), formoterol (NNH 7), and vilanterol (NNH 17). Finally, statistically significantly more patients receiving FSC experienced pneumonia versus those who received budesonide (NNH 13), formoterol (NNH 10), indacaterol (NNH 15), and salmeterol (NNH 19).

Exhibit 6: Results of Network Meta-analysis for Pneumonia

Intervention	Comparison	NNH
ICS+LABA vs. placebo		
Fluticasone + vilanterol	Placebo	10
Fluticasone + salmeterol	Placebo	16
ICS+LABA vs. ICS+LABA		
Fluticasone + salmeterol	Budesonide +formoterol	19
ICS+LABA vs. ICS alone or LABA alone		
Fluticasone + vilanterol	Budesonide	9
Fluticasone + salmeterol	Budesonide	13
Fluticasone + vilanterol	Formoterol	7
Fluticasone + salmeterol	Formoterol	10
Fluticasone + vilanterol	Vilanterol	17
Fluticasone + salmeterol	Indacaterol	15
Fluticasone + salmeterol	Salmeterol	19

Review of other studies for pneumonia

A recent Cochrane review assessed the risk of pneumonia associated with the use of fluticasone and budesonide (alone or in combination with LABA) for COPD.[37] The study authors found a statistically significant increased risk of non-fatal serious pneumonia with fluticasone (alone or in combination with LABA) versus control (OR 1.78, 95% CI 1.50 to2.12); no significant change in the estimate was noted with different doses, trial duration or baseline severity. Budesonide also increased the risk of non-fatal serious pneumonia compared to control (OR 1.62, 95% CI 1.00-2.62), although the data was generated from shorter trials and a significant difference was observed between doses.

Two population-based, propensity score -matched cohort studies in US and Swedish populations suggest that there may be a slightly increased risk of developing pneumonia and dying of pneumonia-related causes among individuals with COPD treated with FSC compared to those using BFC.[32;38]

Arrhythmia

In our network meta-analysis, 17 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 ICS+LABA compared with each other, ICS alone, LABA alone, or placebo.

Commonly reported adverse events

In general, ICS+LABA are well tolerated. In a Cochrane meta-analysis comparing ICS+LABA vs placebo, no significant difference was noted between FSC and placebo in overall adverse events. Pneumonia (odds ratio: OR 1.80, 95% confidence interval: CI 1.49 to 2.18), candidiasis (OR 5.73, 95% CI 3.07 to

10.67), hoarseness (OR 8.79, 95% CI 1.11 to 69.62), nasopharyngitis (OR 1.28, 95% CI 1.05 to 1.56) and upper respiratory tract infection (OR 1.23, 95% CI 1.04 to 1.47) occurred more frequently among patients receiving FSC than placebo. For BFC, no difference was noted between active treatment and placebo for adverse events associated with inhaled corticosteroid use, with the exception of candidiasis.[39]

Pharmacoeconomics Team

Cost-effectiveness Literature Review

A comprehensive search of the literature identified nine studies that were selected for inclusion for the systemic review of published cost-effectiveness studies (Pharmacoeconomics Team Report). Overall, the studies are of limited applicability to the current Canadian setting. Only two studies used effectiveness data from published network meta-analysis or mixed treatment comparison, one study used a published observational cohort study, and many used a single or selection of randomized controlled trials. For some cost-utility analysis, non-utility measures were used to indirectly calculate quality-adjusted life years (QALYs) for many of the cost-utility analyses. All but two studies are industry sponsored;[40;41] results from all manufacturer sponsored economic analyses favoured the manufacturer's treatment.

Only one Canadian study was found. [42] The results of this study suggest that ICS+LABA was more cost effective than LABA alone in patients with Stage 3 COPD (based on the American Thoracic Society criteria), though its cost effectiveness in patients with Stage 2 and Stage 1 was unclear.

Given both contradictory results and the consistent concerns over the quality and the relevance of the available studies, it is not possible to make any inferences on which if any patient population the use of ICS+LABA is cost effective. Therefore, an independent de novo economic model was conducted to address the cost effectiveness of alternative reimbursement strategies for ICS+LABA combination products.

De novo Economic Evaluation

Based on the assumption that there is no difference in efficacy or adverse events between administration of an ICS +LABA via a single inhaler and administration via two separate inhalers, a cost minimization analysis was conducted. In the case of both the budesonide+formoterol combination and the fluticasone+salmeterol combination, the cost of the single inhaler combination product is lower than the cost of receiving the two medications via separate inhalers.

In all severities of COPD, ICS+LABA combination therapy was both more costly and more effective than LABA alone. The incremental cost effectiveness ratio for the ICS+LABA combination versus LABA in patients with at least moderate COPD was $261,539/QALY, in patients with at least severe COPD it was $98,911/QALY and in those with very severe COPD it was $79,448/QALY. With respect to the comparison of the ICS+LABA combination with ICS alone, the combination dominated ICS alone, being both less costly and more effective than ICS alone.

In comparison with LAMA alone, triple therapy is both more costly and more effective resulting in an incremental cost effectiveness ratio ranging from approximately $85,000/QALY to $160,000/QALY. As

compared with LAMA+LABA, triple therapy with an ICS+LABA combination with a LAMA resulted in a cost effectiveness ratio of $28,767 per QALY in patients with at least moderate COPD and triple therapy was the dominant therapy. Interpretation of these latter results should be put into context with the comparative cost effectiveness of the combination of LAMA+LABA versus LAMA alone. In most cases LAMA alone dominated the use of LAMA+LABA as it was both more effective and less costly. Note that any uncertainty in our NMA would affect the results of the pharmacoeconomic analyses. The cost-effectiveness of LAMA alone vs. ICS+LABA will be reported in the upcoming LAMA drug class review.

With respect to both the comparative cost effectiveness of ICS+LABA combination therapy versus ICS alone and LABA alone and the comparison of ICS+LABA combination therapy in addition to LAMA versus LAMA alone and versus LAMA/LABA, the results within each of the subgroups (varied by age and gender) were consistent with those seen in the base case analysis.

Reimbursement-Based Economic Assessment

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 $141.6 million. The largest component of this expenditure was for combination products (i.e., ICS+LABA), which comprised $80.6 million or 57% of drug expenditure. Total costs for combination products including ICS+LABA ranged from $14.3 million for patients with severe COPD to $48.0 million for patients with moderate COPD; for patients with very severe COPD, combination products including ICS+LABA accounted for 60% of drug expenditure or $18.3 million.

The following is a summary of the reimbursement strategies considered:

Limited Use (based on severity of disease)

- Combination ICS+LABA moved to limited use (LU) for COPD
    - Option 1 (OP1): eligible patients include those with at least severe COPD disease
    - Option 2 (OP2): eligible patients include those with at least moderate COPD disease

NOTE:

- Costs were estimated by assuming 20% of current users on triple therapy (i.e., ICS, LABA and LAMA) or dual therapy (ICS and LABA) would move to combination therapy (ICS+LABA plus LAMA, or ICS+LABA, respectively).
- All patients currently on combination therapy would remain on combination therapy.

Limited Use (based on severity of disease and preferred listing)

- Advair Diskus moved to limited use (LU) for COPD (preferred therapy)
    - Option 3A (OP3A): eligible patients include those with at least severe COPD disease
    - Option 4A (OP4A): eligible patients include those with at least moderate COPD disease
- Symbicort moved to limited use (LU) for COPD (preferred therapy)
    - Option 3S (OP3S): eligible patients include those with at least severe COPD disease
    - Option 4S (OP4S): eligible patients include those with at least moderate COPD disease

NOTE:

- Costs were estimated by assuming 20% of current users on triple therapy (i.e., ICS, LABA and LAMA) or dual therapy (ICS and LABA) would move to combination therapy (ICS+LABA plus LAMA, or ICS+LABA, respectively).
- All patients currently on combination therapy would remain on combination therapy.
- A 20% price reduction for preferred listing drug was applied.
- The non-preferred drug was not listed on the ODB formulary.

Limited Use (based on severity of disease, preferred listing and Exceptional Access Program (EAP) listing of non-preferred drug)

- Advair Diskus moved to limited use (LU) for COPD (preferred therapy)
    - Option 5A (OP5A): eligible patients include those with at least severe COPD disease
    - Option 6A (OP6A): eligible patients include those with at least moderate COPD disease
- Symbicort moved to limited use (LU) for COPD (preferred therapy)
    - Option 5S (OP5S): eligible patients include those with at least severe COPD disease
    - Option 6S (OP6S): eligible patients include those with at least moderate COPD disease

NOTE:

- Costs were estimated by assuming 20% of current users on triple therapy (i.e., ICS, LABA and LAMA) or dual therapy (ICS and LABA) would move to combination therapy (ICS+LABA plus LAMA, or ICS+LABA, respectively).
- All patients currently on combination therapy would remain on combination therapy.
- A 20% price reduction for preferred listing drug was applied.
- The non-preferred drug was listed as an EAP drug.

Exhibit 7: Summary of Budget Impact Analysis

Options for Reimbursement		Total Costs and Impact on COPD Budget*		% Budget Impact
Current Total Reimbursement of all COPD therapy			$141,599,030	
Advair and Symbicort moved to Limited Use				
OP1	At Least Severe	Expected total $	$141,581,490	**↓ 0.01%**
		Budget impact	-$17,540	
OP2	At Least Moderate	Expected total $	$141,550,754	**↓ 0.03%**
		Budget impact	-$48,277	
Advair Diskus (preferred listing) moved to Limited Use				
OP3A	At Least Severe	Expected total $	$138,012,318	**↓ 2.5%**
		Budget impact	-$3,586,713	
OP4A	At Least Moderate	Expected total $	$133,012,348	**↓6.1%**
		Budget impact	-$8,586,683	
Symbicort (preferred listing) moved to Limited Use				
OP3S	At Least Severe	Expected total $	$140,211,068	**↓ 0.98%**
		Budget impact	-$1,387,963	
OP4S	At Least Moderate	Expected total $	$137,835,270	**↓ 2.7%**
		Budget impact	-$3,763,760	
Advair Diskus (preferred listing) moved to Limited Use (Symbicort on EAP)				
OP5A	At Least Severe	Expected total $	$138,004,334	**↓ 2.5%**
		Budget impact	-$3,594,697	
OP6A	At Least Moderate	Expected total $	$132,993,680	**↓ 6.1%**
		Budget impact	-$8,605,351	
Symbicort (preferred listing) moved to Limited Use (Advair Diskus on EAP)				
OP5S	At Least Severe	Expected total $	$140,213,461	**↓ 0.98%**
		Budget impact	-$1,385,570	
OP6S	At Least Moderate	Expected total $	$137,839,359	**↓ 2.7%**
		Budget impact	-$3,759,671	

*Total COPD expenditures by OPDP in 2012: includes ICS, LABA, LAMA and ICS+LABA therapies

Summary

Since the cost of ICS+LABA combination therapy is less expensive than ICS and LABA dual therapy and as many patients with COPD are already receiving ICS+LABA combination therapy using the LU code (code 330) for asthma, there is minimum impact on COPD total costs if Advair and/or Symbicort are moved to Limited Use.

Health Equity Issues

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

Accessibility of ICS+LABA combination products

Despite the lack of coverage of ICS+LABA for COPD in Ontario, no accessibility issues were identified in our review. In fiscal 2012, 62.6% of all patients prescribed combination products had a diagnosis of COPD (both with and without a concurrent diagnosis of asthma); almost one-third (28%) of provincially-funded combination product users had a diagnosis of COPD with concurrent asthma. In our one-on-one interviews, it was noted that physicians often resort to using the Limited Use (LU) code 330 for asthma to access these drugs for their patients. However, not all physicians use the asthma code which means that some patients with COPD who are eligible for ODB benefits may not be receiving ICS+LABA combination therapy. For patients under the age of 65 and without public or private coverage, access to COPD medications including ICS+LABA may be a challenge as ICS+LABA cost approximately $60-145/month.

Use in elderly

Overall, utilization of ICS+LABA was higher among older patients with COPD which is likely driven by the prevalence of COPD and ODB eligibility criteria. Our analysis found that COPD patients prescribed ICS+LABA tended to be over 65 years of age, have moderate COPD severity, and live in urban locations.

Use in Women

In Ontario, approximately 850,000 individuals had a diagnosis of COPD in 2008, of whom 50.6% were female.[8] Analysis of Ontario data showed that use of ICS+LABA was slightly more common among women (approximately 54% of all users).

Reimbursement Options for Consideration

Key Considerations

Efficacy

- Overall, ICS+LABA combination products have been shown to reduce exacerbation rates and improve lung function and quality of life. ICS+LABA products were found to be more effective than other long-acting inhaled therapies for COPD, including LABAs, LAMAs and ICS products.
- When ICS+LABA products were compared with each other, the two ICS+LABA agents with the highest probability of being the most effective for decreasing risk of COPD exacerbation in patients with moderate COPD were BFC and MFC.

Safety and tolerability

- An increased risk of pneumonia has been attributed to ICS, either alone or in combination with LABA.
- Although no head-to-head randomized controlled trials have been done comparing BFC and FSC,

evidence suggests that fluticasone, alone or in combination with a LABA, is associated with a greater risk of pneumonia than placebo, budesonide (alone or in combination with a LABA) or LABA.

- For the safety outcome of arrhythmias, no statistically significant differences were observed across any of the ICS+LABA agents compared with each other, ICS alone, LABA alone, or placebo.
- The balance between the risks and benefits of ICS+LABA combination products must be carefully considered.

Accessibility

- Despite the lack of coverage of ICS+LABA products for COPD in Ontario, no accessibility issues were identified in our review. In our one-on-one interviews with respirologists and primary care physicians, it was noted that physicians often resort to using the Limited Use (LU) code 330 for asthma to access these drugs for their patients. If Limited Use for ICS+LABA products would include criteria for COPD coverage, this could impact accessibility of these products to all patients with COPD.
- For patients under the age of 65 and without public or private coverage, access to COPD medications including ICS+LABA may be a challenge.

Pharmacoeconomics

- If triple therapy (LAMA plus ICS plus LABA, as separate inhalers) and dual therapy (ICS plus LABA, as separate inhalers) users moved to combination product (ICS+LABA) and assuming COPD patients already on ICS+LABA would remain on combination therapy, there would be a small absolute reduction in expenditure by OPDP (approximately $48,000 or a reduction of 0.03%).
- In patients receiving ICS and LABA via separate inhalers, our de novo economic evaluation supports the cost effectiveness of moving to administration of the combination via a single inhaler. The incremental cost per QALY gained for ICS and LABA when compared with LABA alone ranged from $80,000 to $260,000 dependent on the severity of disease. The incremental cost per QALY gained for triple therapy with ICS+LABA combination in addition to LAMA compared with LAMA alone ranged from $85,000 to $160,000 dependent on the severity of disease.

Reimbursement Options

Reimbursement options for ICS+LABA (for asthma and COPD indications) will be reviewed at the completion of the drug class reviews for LAMA for COPD and ICS+LABA for asthma (approximately November 2014).

Conclusion

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

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Appendix A: Health Equity Considerations for ICS+LABA 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 ICS+LABA 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 ICS+LABA 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 ICS+LABA) 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 ICS+LABA 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/)