

Inhaled Corticosteroids (ICS) + Long-Acting Beta-Agonists (LABA) for the Treatment of Asthma



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 (MOHLTC) 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.

Tara Gomes received grant funding from the Ministry of Health and Long-term Care.

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 Asthma 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 Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).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

ACT	Asthma Control Test
ACQ	Asthma Control Questionnaire
BC	British Columbia
BFC	Budesonide + formoterol combination
CADTH	Canadian Agency for Drugs and Technologies in Health
CDEC	Canadian Drug Expert Committee
CIHI	Canadian Institute for Health Information
COPD	Chronic obstructive pulmonary disease
CI	Confidence interval
FEV1	Forced expiratory volume in 1 second
FSC	Fluticasone propionate + salmeterol combination
FVC	Fluticasone furoate+ 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
LTRA	Leukotriene receptor antagonist
LU	Limited Use
MFC	Mometasone + formoterol combination
MOHLTC	Ministry of Health and Long-term Care
NIHB	Non-insured Health Benefits
NNT	Number needed to treat
NS	Not statistically significant
NT	Northwest Territories
NU	Nunavut
ODB	Ontario Drug Benefit
ODPRN	Ontario Drug Policy Research Network
OPDP	Ontario Public Drug Programs
OR	Odds ratio
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
SMH	St. Michael's Hospital
UK	United Kingdom

Executive Summary

In Canada, there are four inhaled corticosteroid and long-acting beta-agonist (ICS+LABA) combination products available: fluticasone propionate + salmeterol (FSC: Advair), budesonide + formoterol (BFC: Symbicort), fluticasone furoate + vilanterol (FVC: Breo Ellipta), and mometasone + formoterol (MFC: Zenhale). Advair and Symbicort are indicated for both the management of asthma and chronic obstructive pulmonary disease (COPD), Zenhale for the management of asthma and Breo Ellipta for the management of COPD. All products, except for FVC, 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 for management of asthma was undertaken to provide recommendations for funding of these products in Ontario for asthma. Long-acting muscarinic agents (LAMAs) for COPD and ICS+LABA for COPD have been reviewed by Ontario Drug Policy Research Network (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.

Key Considerations for Reimbursement Options

Efficacy and Safety

A rapid systematic review was conducted to examine the available evidence with respect to clinical outcomes for long-acting inhaled therapies commonly used to treat asthma in patients 12 years of age and older. A network meta-analysis showed that fixed or adjustable dose combined inhalers with low dosage ICS+LABA, medium dosage ICS+LABA, or high dosage ICS+LABA had the greatest probability of decreasing the risk of moderate to severe exacerbations when compared to other long-acting therapies such as LABAs alone, leukotriene receptor antagonists (LTRAs) or ICS alone. Neither a network meta-analysis nor a meta-analysis was completed for symptom-scales as only two included randomized controlled trials (RCTs) reported on this outcome; neither trial reached a clinically relevant important difference.

There were no significant differences in risk of cardiovascular disease or cardiovascular-related mortality across all treatment groups.

Accessibility

In Ontario, ICS+LABAs are available on the ODB formulary as Limited Use for patients with asthma. As such, no accessibility issues for qualifying patients, including those aged 65 years and older, were identified in our review. For patients under the age of 65 and without public or private coverage, access to asthma medications including ICS+LABA may be challenging as these drugs can cost \$60-140/month.

Pharmacoeconomics

The de novo economic evaluation found that the later LABA was introduced into therapy, the more cost-effective the treatment strategy became. Therefore, the optimal strategy was found to be the

introduction of LABA to patients when they were uncontrolled with high doses of ICS.

A policy of not funding either low dose ICS+LABA combination products or low and medium dose ICS+LABA combination products would generate costs savings ranging from \$0.4 to \$4M. However, if such policies lead to a substantial proportion of patients (approximately 50%) uncontrolled on ICS moving to higher dose ICS+LABA combination products instead of higher dose ICS monotherapy, no savings will arise (increase in cost of \$2M).

Reimbursement Options

Final recommendations for the funding of ICS+LABA for asthma through the publicly funded drug program in Ontario are found in a companion report: Final reimbursement options-- Select drug therapies for treatment of chronic obstructive pulmonary disease and asthma (available on www.odprn.ca).

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Rationale for Review

In Canada, there are four inhaled corticosteroid and long-acting beta-agonist (ICS+LABA) combination products available: fluticasone propionate + salmeterol (FSC: Advair), budesonide + formoterol (BFC: Symbicort), fluticasone furoate + vilanterol (FVC: Breo Ellipta), and mometasone + formoterol (MFC: Zenhale). Advair and Symbicort are indicated for both the management of asthma and COPD, Zenhale for the management of asthma and Breo Ellipta for the management of COPD. All products, except for FVC, 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 asthma and COPD was undertaken to provide recommendations for funding of these products in Ontario. As well, the long-acting muscarinic agents (LAMAs) for COPD were reviewed by ODPRN as a separate drug class review. Due to overlapping themes, final policy recommendations for all three drug classes will be released upon completion of the three reviews.

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: www.odprn.ca

Background Information

Asthma is an inflammatory disorder of the airways characterized by paroxysmal or persistent symptoms such as dyspnea, chest tightness, wheezing, sputum production and cough, associated with variable airflow limitation and airway hyperresponsiveness to endogenous and exogenous stimuli.¹ Asthma affects approximately 2.3 million Canadians over the age of 12.² In Ontario in 2005, there were 1.7 million people (12.8% of the population) who had been diagnosed with asthma.³

The primary goal of asthma management is to control the disease and prevent or minimize risk of short- and long-term complications, morbidity and mortality. However, numerous barriers to managing the disease effectively are still present including underdiagnosis, especially in children, inaccurate perception of control of disease, and nonadherence to management plans.⁴ Treatment of asthma includes nonpharmacologic (e.g., trigger avoidance, environmental control, reduction of allergen exposure) and pharmacologic therapies. Inhaled corticosteroids (ICS) are the cornerstone of chronic maintenance pharmacotherapy for patients with asthma of all ages. For children 6 years of age and older and adults, leukotriene receptor antagonists (LTRAs) are second-line agents that can be used as monotherapy. In patients who remain uncontrolled on ICS monotherapy, increasing the dose of the ICS, adding a long-acting beta2-agonist (LABAs) or adding an LTRA are options.¹ For patients 12 years of age and older who remain uncontrolled on low-dose ICS, the addition of a LABA is recommended, ideally in the form of a combination inhaler.⁵

According to the Ontario Lung Association, it is estimated that the direct healthcare costs of asthma care in Ontario in 2011 was \$1.6 billion.⁶ The major costs associated with direct health-care related costs

include medications, physician visits and hospitalizations.⁷ Indirect costs are mainly due to time loss from work, productivity loss, functional impairment and caregiver time also contribute to the economic burden.⁸ As well, patients with poorly controlled asthma are responsible for the majority of asthma-related resource use.⁹ In a survey conducted in Canada, asthma control and management remained suboptimal with approximately 50% of patients with uncontrolled asthma.¹⁰ Although there is limited data on the humanistic burden of asthma, studies show a high (31-50%) prevalence of psychological distress and diminished quality of life among asthma patients relative to patients without asthma.⁸

Public plan reimbursement of ICS+LABA products in Canada

In Ontario, three 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 (LU code 330: For the treatment of asthma in patients who are using optimum anti-inflammatory treatment and are still experiencing breakthrough symptoms).

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 asthma (for public plan listings, see Exhibit 1). Restriction criteria vary slightly across the public drug programs. In two provinces (Alberta and Manitoba), Advair and Symbicort are listed as general benefits (Zenhale is listed in Manitoba as a general benefit). Inadequate response to optimal dose of inhaled corticosteroid is considered a prerequisite for approval of ICS+LABA products in most jurisdictions. Other restriction criteria include optimum use of anti-inflammatory treatment and still experiencing breakthrough symptoms, and stabilized on inhaled corticosteroid plus a long-acting beta2-agonist. Note: in all public drug programs across Canada except for Ontario, at least one of the ICS+LABA products is funded for the management of patients with COPD.

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	Ben	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 Canadian Drug Expert Committee (CDEC) recommendations were posted in August 2014.

Current as of February 23, 2015.

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

Objective

The objective of the ICS+LABA for asthma drug class review is to provide evidence-informed recommendations for the funding of ICS+LABA products for asthma through the publicly funded drug program in Ontario. ICS+LABA for COPD and LAMAs for COPD are 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 ICS+LABA for asthma 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 asthma
- 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

Challenges in Asthma Management

Challenges in asthma management were described by both patients and clinicians, although this theme primarily emerged from the clinician participants. The high cost of medications, fear of regular steroid use, lack of education about the purpose of maintenance medications, and poor perception of asthma control were all described by participants as barriers.

Clinician participants described that the cost of maintenance medications such as ICS+LABA are \$100-

\$200 a month on average, and that patients who do not have drug coverage are less likely to comply with their prescribed medication. Instead of using maintenance medications, patients may be relying heavily on rescue medications, which are significantly less expensive.

Nearly all clinician participants explained that some patients can be hesitant about the regular use of medications such as ICS+LABA that contain an inhaled steroid. Their patients have expressed concerns about growth stunting in children, and various side effects that are commonly associated with systemic steroids such as prednisone. Clinicians perceived there to be a misconception about inhaled steroids and some have tried to mitigate this by educating and counseling their patients. In addition, some patient participants described that they did not understand the purpose of the ICS+LABA and other maintenance medications and this has affected their adherence.

“Patients don’t like taking medications. Sometimes they are fearful of the steroid...They may not believe that they need it, you know. Just because I tell them they need it doesn’t mean that they believe they need it.” –Respirologist

*“I feel like my asthma is more under control than it was when I was a lot younger, although, from a clinical practice guideline perspective, it’s not. I just am lazy and don’t take the Advair. I often don’t remember to take it. You know I think it’s, out of sight out of mind. If you are not always having symptoms, then you are not thinking to take a preventive thing each day because you are thinking well, is that really working? Is it really something that’s useful, given the side effects?”—
Patient*

Influences on the Prescription of Asthma Medications

Various factors may influence a physician’s decision to prescribe ICS+LABA medications including; adherence to guidelines and recent research evidence, the ease of use of products, patient affordability and the availability of products on the Ontario Drug Benefit formulary.

Physician participants referred to the Canadian asthma guidelines, which have guided their step-wise approach to care including the prescription of ICS+LABA for moderate or severe patients. In addition, participants said that they incorporate evidence from specific research studies to influence their decisions on prescribing. Ease of administration was an important factor considered by clinician participants when prescribing ICS+LABA. In general, Diskus (i.e., Advair Diskus) and Metered Dose (i.e., Advair, Zenhale) Inhaler products were described as the easiest to use. Some clinicians preferred to put their patients on the same type of device for all medications. The Turbuhaler (i.e., Symbicort) was described as the most cumbersome to use. Clinicians and patient participants also described that patients may be more likely to comply with once-a-day therapy.

Perception of Asthma Medication

Patients generally wished to have an appropriate balance of benefits and inconveniences such as side effects and multiple doses. Patients described that their wish is to have medication that enables maximal bronchodilation so they can breathe easily as well as carry on with various activities such as travelling, exercise and socializing. Some expressed a desire to take only one medication, to reduce dosages or to discontinue steroid containing medications. Participants had mixed perceptions of the impact of ICS+LABA on their quality of life. Many of them were on multiple medication regimens and found it challenging to comment specifically on the effects of their ICS+LABA medications.

“I don’t really feel like it has improved my quality of life. It could be because I’m non-compliant, but I think there are other things that I’ve done to better manage my asthma in the first place rather than needing to take a corticosteroid.”—Patient

Accessibility of ICS+LABA for Asthma

Access to ICS+LABA is not an issue for ODB eligible patients because physicians use the asthma LU code. Those under the age of 65 years, who are not ODB eligible and who do not have access to third party coverage, may have significant financial barriers to accessing ICS+LABA products because of their cost. Physicians have used various strategies to mitigate barriers such as providing samples and hiring social workers to assist patients.

“Often they don’t know about the Trillium plan but once you tell them about the Trillium plan, it is,... it’s a disorganized chaotic life, they’ve not filed their income taxes, they’ve been struggling to pay the next bill, they live from, you know ,rent cheques to rent cheques, or mortgage payments to mortgage payments... . They’re stressed, they’ve got kids, they’re two working parents and they’re stressed to the limits and they haven’t taken the time to figure out all of these things.”—

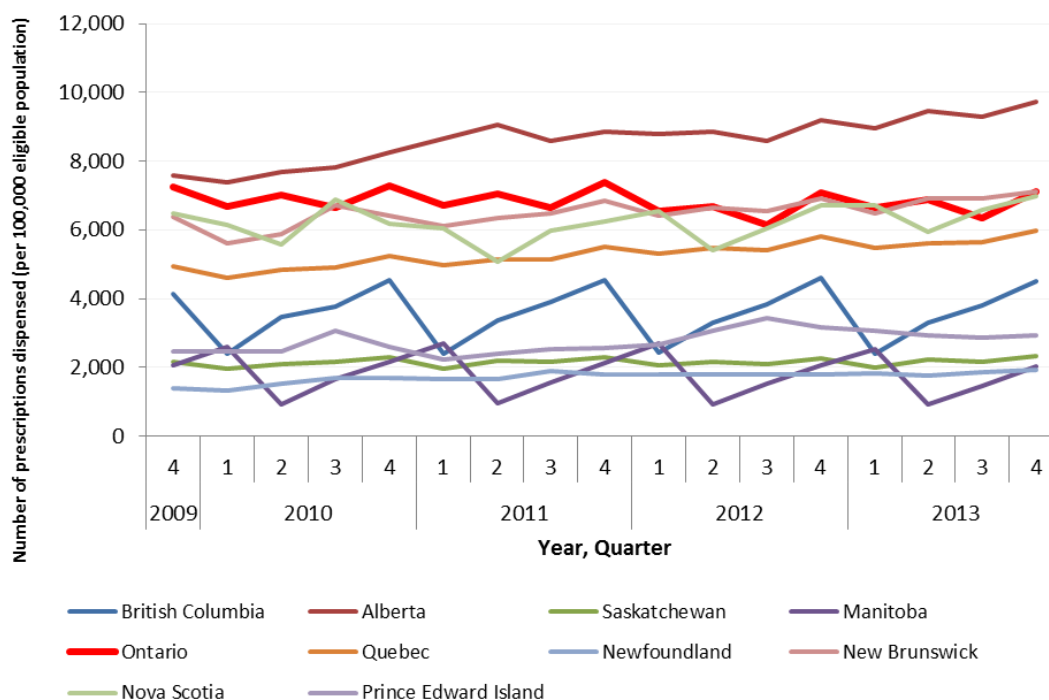
Respirologist

Pharmacoepidemiology Team

Current Utilization in Canada and Ontario

ICS+LABA combination products are the second most commonly prescribed anti-inflammatory and bronchodilator agents (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 combination products dispensed in Canada were for Advair. 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 combination products (7,127 prescriptions dispensed per 100,000 eligible population vs. national average of 5,063 prescriptions dispensed 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).

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



In public drug plan beneficiaries with asthma in 2012, ICS+LABA combination products were the third most commonly prescribed therapy among youth aged 12 to 17 (following SABA and ICS therapies), the

second most commonly prescribed therapy among adults aged 18 to 64 (following SABA therapy) and the most commonly prescribed therapy among older adults (aged 65 years and older) (Exhibit 3). Among individuals with asthma, the number of ICS+LABA combination product users has increased nearly 23-fold across all age groups, between their introduction in 2000 and 2012. By 2012, among individuals with asthma, the majority (71%) of ICS+LABA combination products were being used by older adults (Exhibit 4). The rate of ICS+LABA combination product users has also increased over time across all age groups (between 2000 and 2013), however a decline in the rate of users among youth and young adults was observed between 2011 and 2013.

Exhibit 3: Total utilization of asthma therapy products among public drug plan beneficiaries with asthma in Ontario, age 65+, by product and fiscal year

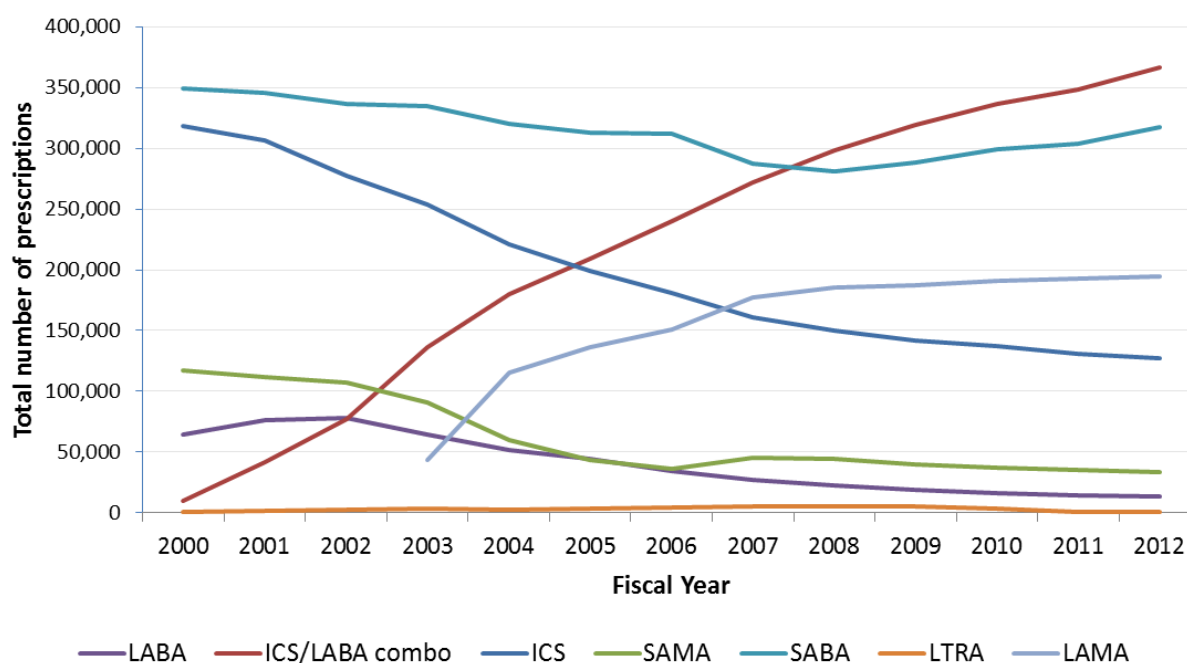
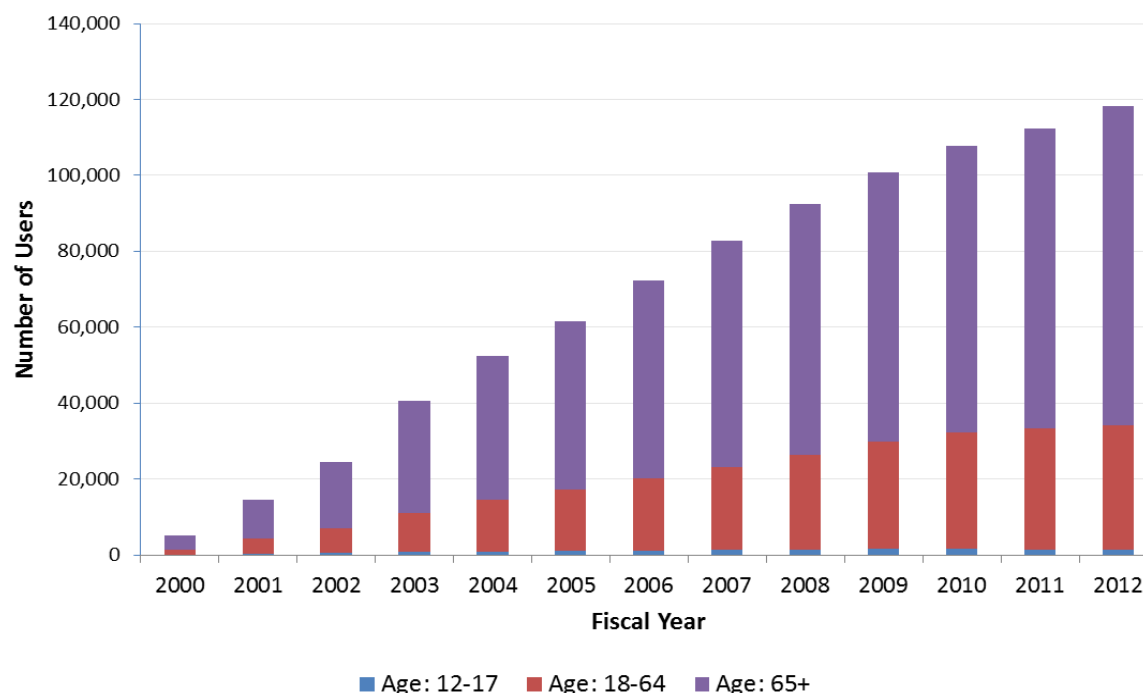


Exhibit 4: Number of users of provincially-funded ICS+LABA combination products with asthma in Ontario, by age and fiscal year



In fiscal year 2012, 111,064 asthma patients aged 12 and older, received provincially-funded ICS+LABA combination products in Ontario. The majority (64.2%) of youth (aged 12-17) were new ICS+LABA users compared to 44.9% of young adults (aged 18-65) and 22.8% of older adults (over 65 years of age). Youth users experienced more asthma exacerbations in the previous year, compared to younger adults and older adults (10.1%, 5.8% and 2.1%, respectively).

The most common concomitant asthma therapy among all groups was SABAs (60-70% of all users). The prevalence of therapy with ICS+LABA plus LAMA was highest among older adult patients (40-50%) compared to youth and adult patients (<1% and 20-30%, respectively) in fiscal year 2012. 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 FEV₁.¹¹⁻¹³

Adherence

The findings of our analysis in Ontario found that among ODB-eligible asthma patients initiating combination therapy with ICS+LABA, only 20-30% of youth, 30-50% of young adults and 40-50% of older adults were considered adherent to therapy after one year. Two observational studies assessed adherence to therapy, with one study finding a significant difference in favour of BFC, while a second

study observed no difference between agents.^{14, 15}

Rapid Review Team

Efficacy

Outcome measures used for assessment of treatment options in asthma include measures of pulmonary physiology (e.g., spirometry), exacerbations, composite scores (e.g., Asthma Control Questionnaire (ACQ) or Asthma Control Test (ACT)), and quality of life and symptoms.¹⁶ Two efficacy outcomes were used for analysis in our report: exacerbations (primary efficacy outcome) and patient's asthma control (secondary efficacy outcome).

Exacerbations

In our review, 46 randomized controlled trials (RCTs) at least 24 weeks of treatment duration reported on moderate to severe exacerbations and included 35,012 patients (12 years or greater) with asthma.

Results of our ranking analysis for exacerbations for patients with asthma

For patients with chronic asthma aged 12 years or greater, ICS+LABA (regardless of dosage, adjustable or fixed dosing) had the largest probability of being the most effective for decreasing risk of moderate to severe exacerbations in comparison to other long-acting inhaler agents such as ICS, LTRA and LABAs (either alone or in combination) (see Exhibit 5).

Exhibit 5: Results of network meta-analysis for risk of exacerbation in patients with asthma

Placebo								
LABA	NS							
ICS low dose	NS	NS						
ICS medium dose	NS	NS	NS					
ICS high dose	NNT 5	NS	NS	NS				
ICS low dose + LABA*	NNT 3	NNT 3	NNT 5	NS	NS			
ICS medium dose + LABA*	NNT 3	NNT 3	NNT 5	NNT 6	NS	NS		
ICS high dose + LABA*	NNT 3	NNT 3	NNT 4	NNT 5	NS	NS	NS	
	Placebo	LABA	ICS low dose	ICS medium dose	ICS high dose	ICS low dose + LABA*	ICS medium dose + LABA*	ICS high dose + LABA*

*ICS+LABA combined in one inhaler, fixed corticosteroid dosage

NS: Not statistically significant

NNT: Number needed to treat. NNT calculated using the odds ratio from the meta-analysis whenever network meta-analysis was not statistically significant.

- The green block indicates that the 'row' treatment is significantly better than the 'column' treatment.
- The grey block indicates that there is no significant difference between the 'row' and 'column' treatment.

Patient's Asthma Control

No conclusions can be made on patient's asthma control using the ACT scale, as only two RCTs reported on this outcome. Neither study reached the clinically relevant important difference on the ACT.

Review of Other Studies

Exacerbations and Hospitalizations

Observational studies: Two studies conducted in the UK^{14;15} reported no significant difference in rates of exacerbations (using hospitalizations) in patients with asthma using BFC or FSC. However, significant differences between treatment groups, favouring BFC, were found among the two studies conducted outside of the UK.^{17;18} A Canadian cohort study (N=1,264 FSC and N=1,264 BFC) using data from Quebec found that BFC users were less likely to have severe exacerbations compared to FSC (Rate ratio = 0.72; 95% CI 0.54 to 0.96).¹⁸ The findings from these studies are not consistent. Results of these studies should be interpreted with caution due to the possible impact of systematic differences in comparison groups leading to bias.

Network meta-analysis: A network meta-analysis, which included 57 trials with 53,309 patient years of follow-up, found that combined ICS and LABA as maintenance and reliever treatment and combined ICS and LABA in a fixed daily dose had the greatest probability of being the most effective for reducing severe exacerbations when compared to low dose inhaled corticosteroids in an adult population.¹⁹

Asthma Control (measured via SABA use)

Four observational studies reported on asthma control with use of ICS+LABA.^{14;15;17;18} All four studies used SABA utilization as the surrogate to assess control using different definitions to define control. Three of the included studies showed better control with the use of BFC. A fourth study showed no difference between BFC and FSC. Use of SABA is often a good indicator of asthma control but varying definitions between studies does not allow for easy comparability of studies.

Safety and Tolerability

Cardiovascular disease and cardiovascular-related mortality

Network meta-analysis was conducted for the safety outcome of "cardiovascular diseases". Only three RCTs including 1,527 patients were included. No statistically significant differences in risk of development of cardiovascular disease were noted. For the safety outcome of "cardiovascular-related mortality", no statistically significant differences were observed in a meta-analysis comparing ICS versus ICS+LABA, fixed dosage.

Review of Other Studies

Cardiovascular safety

A systematic review was published to assess the available evidence on the cardiovascular safety of ICS+LABA in adults with asthma. A total of 15 studies were identified of which two studies with BFC and one with FSC reported treatment-emergent cardiovascular adverse events, namely dysrhythmias. A nonsignificant difference between ICS+LABA and comparator/placebo groups was noted (risk ratio 0.77; 95% CI 0.26 to 2.30).²⁰

Asthma-related mortality

Regular use of beta2-agonists (as monotherapy) in patients with asthma has shown to lead to increased asthma mortality.^{21;22} However, LABA in combination with ICS has not been shown consistently to result in similar increased asthma mortality. A meta-analysis was conducted that included trials of patients of any age or severity of asthma receiving treatment with regular salmeterol and ICS. No statistically significant differences in fatal or non-fatal serious adverse events was observed in patients receiving salmeterol+ICS or ICS alone. Another systematic review and meta-analysis evaluated treatment with regular formoterol and ICS. In adults for all-cause mortality, the pooled Peto odds ratio was 3.56 (95% CI 0.79 to 16.03). However, since only one death was attributed to asthma, the evidence was insufficient to allow assessment of asthma-related mortality. No significant difference in non-fatal serious adverse events was noted with formoterol and ICS, although a significant reduction in asthma-related serious adverse events was seen in comparison with ICS alone.²³ A systematic review and meta-analysis of non-randomized studies (including observational studies) showed that ICS+LABA compared to ICS alone is not associated with a higher risk of serious adverse events (OR 0.95; 95% CI 0.9 to 1.0).²⁴

Pharmacoeconomics Team

Cost-Effectiveness Literature Review

A total of sixteen reports were identified for inclusion in the review. The majority were European studies (UK, Sweden, Netherlands, Denmark, Germany, and Spain), two were Canadian studies, and one was an American study. A total of nine studies were cost-effectiveness analyses, four were cost-utility analyses, two were both cost-effectiveness and cost-utility analyses, and one was a cost-effectiveness and cost-consequence analysis.

One independent Canadian study, which was sponsored by CADTH, was a cost-effectiveness/utility analysis of LABA in addition to ICS compared to ICS alone in adolescents and adults with asthma.²⁵ Patients were divided in one of three categories: steroid naïve patients, low dose ICS users, and medium dose ICS users. Within this study, the incremental cost utility ratios for ICS plus LABA compared to ICS alone ranged from \$0.19 million to \$3.3 million per quality adjusted life year (QALY) gained. Thus, a strategy of adding LABA to ICS would only be cost-effective in patients who were uncontrolled on high dose ICS. For patients with poor control on lower dose ICS, increasing the dose of ICS would be more cost effective than adding a LABA. This study did not include costs associated with adverse events, or a comparison of specific ICS+LABA and ICS therapies. In addition, as it was published in 2008, is not reflective of the current evidence base.

An independent UK study conducted by Lenney and associates compared the cost-effectiveness of ICS+LABA (fluticasone propionate 100 µg/salmeterol 50 µg twice a day) to ICS (fluticasone propionate 100 µg twice a day plus placebo once a day) in children with asthma aged 6-14.²⁶ The incremental cost-utility ratio of ICS+LABA compared to ICS alone was £12,054 per QALY gained. However, the restrictive trial population makes it difficult to generalize to a wider patient population. In addition, this study

compared the same dose of ICS with and without the addition of a LABA rather than a reduced dose of ICS with LABA. The study concluded that it was not possible to determine whether adding a LABA to those receiving ICS can reduce the number of exacerbations in children with uncontrolled asthma.

Given the limitations of one of the studies and the need to incorporate more recent evidence, a de novo economic model is required to assess the cost-effectiveness of ICS+LABA compared to ICS alone using recent data from the Canadian context.

De novo Economic Evaluation

A cost-utility analysis (CUA) was conducted from the perspective of a provincial ministry of health. Effectiveness was assessed in the form of QALYs with a one year time horizon. Analysis was based on a Markov cohort model developed to predict the outcomes of each of the pharmaceutical management strategies. Four distinct strategies were considered. The strategies relate to the time point at which ICS+LABA combination products are adopted: for patients who are naïve to ICS (Strategy 1), after lack of control on low dose ICS (Strategy 2), after lack of control on moderate dose ICS (Strategy 3) and after lack of control on high dose ICS (Strategy 4).

The model used data from the companion systematic review, a previous Canadian HTA and appropriate sources for costs and utility values. Detailed deterministic and probabilistic sensitivity analyses were also conducted.

The incremental cost-utility ratio (ICUR) decreases the later a LABA is introduced into therapy for analysis at 1 year. The incremental cost per QALY gained from initiating treatment with a LABA plus ICS rather than introducing LABA after lack of control on low dose ICS monotherapy is \$1.27 million. The incremental cost per QALY gained from introducing LABA after lack of control on low dose ICS monotherapy compared to introducing it after lack of control on medium dose ICS monotherapy is \$410,963. Finally, the incremental cost per QALY gained from introducing LABA after lack of control on medium dose ICS monotherapy compared to introducing it after lack of control on high dose ICS monotherapy is \$332,684.

For threshold values for a QALY up to \$100,000 the probability that strategy 4 (adding LABA to patients uncontrolled on high dose ICS) is optimal is 100%. For all threshold values between \$100,000 and \$200,000, the probability that either Strategy 1 (adding LABA to treatment naïve patients), Strategy 2 (adding LABA to patients uncontrolled on low dose ICS), or Strategy 3 (adding LABA to patients uncontrolled on medium dose ICS) are optimum is never greater than 10%.

The economic analysis found that the later LABA was introduced into therapy, the more cost-effective the treatment strategy became. Thus, the optimal strategy considered was introducing LABA to patients when they were uncontrolled with high doses of ICS.

Budget Impact Analysis

Total OPDP expenditure on asthma therapy (ICS, LABA, ICS+LABA and LAMA) was \$112.6 million (from

April 2012 to March 2013), with ICS+LABA combinations comprising 64% (\$72.5 million). Assuming a policy whereby combination products involving low dose ICS+LABA are not funded and assuming all patients uncontrolled on low dose ICS move to medium dose ICS, this would lead to a small absolute reduction in total asthma therapy expenditure (savings of \$0.4 million). Smaller cost savings are expected however, if half of the patients uncontrolled on low dose ICS move to medium dose ICS+LABA (savings of \$87.3 thousand).

Assuming a policy whereby combination products involving low and medium dose ICS+LABA are not funded and assuming all patients uncontrolled on low dose ICS move to medium dose ICS and patients uncontrolled on medium dose move to high dose ICS, this would lead to greater savings (a reduction of \$4.4 million). However, if half of the patients uncontrolled on medium dose ICS move to high dose ICS+LABA costs will increase (an increase of \$2.1 million).

Assuming a policy of not funding low and medium dose ICS+LABA combination products would lead to the greatest savings. However, under a scenario where 50% of patients uncontrolled on moderate ICS move to a high dose ICS+LABA combination product, not funding alternate dose ICS+LABA combination products may lead to increased costs.

Exhibit 6: Budget impact: alternative approached to reimbursement

REIMBURSEMENT SCENARIO	IMPACT	TOTAL [^]	% BUDGET IMPACT
Status quo:			
Current reimbursement		\$112,557,431	
BASE CASE			
STRATEGY #1 –No coverage of low dose ICS+LABA			
Coverage of ICS+LABA only after trial of medium dose ICS	Expected total \$	\$112,142,990	
	Budget impact	-\$414,441	↓ 0.37%
STRATEGY #2 –No coverage of low or medium dose ICS+LABA			
Coverage of ICS+LABA only after trial of high dose ICS	Expected total \$	\$108,175,938	
	Budget impact	-\$4,381,494	↓ 3.89%
SENSITIVITY ANALYSIS			
STRATEGY #1B –No coverage of low dose ICS+LABA			
Coverage of ICS+LABA only after trial of medium dose ICS (50% to medium dose ICS and 50% to medium dose ICS+LABA)	Expected total \$	\$112,470,054	
	Budget impact	-\$87,377	↓ 0.08%
STRATEGY #2B – No coverage of low or medium dose ICS+LABA			
Coverage of ICS+LABA only after trial of high dose ICS (50% to high dose ICS and 50% to high dose ICS+LABA)	Expected total \$	\$114,627,302	
	Budget impact	+\$2,069,870	↑ 1.84%

[^]Data from April 2012 to March 2013

Summary

Review of Economic Literature: Given the limitations of the published studies and the need to incorporate more recent evidence, a de novo economic model was completed to assess the cost-effectiveness of ICS+LABA compared to ICS alone using recent data from the Canadian context.

De novo Economic Evaluation: The de novo economic evaluation found that the later LABA was introduced into therapy, the more cost-effective the treatment strategy became. Therefore, the optimal strategy considered was introducing LABA to patients when they were uncontrolled with high doses of ICS.

Budget Impact Analysis: A policy of not funding either low dose ICS+LABA combination products or low and medium dose ICS+LABA combination products would generate costs savings ranging from \$0.4 to \$4M. However, if such policies lead to a reasonable proportion of patients (approximately 50%) uncontrolled on ICS moving to higher dose ICS+LABA combination products instead of higher dose ICS monotherapy, no savings will arise (increase in cost of \$2M).

Health Equity Issues

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

Accessibility of ICS+LABA products

No accessibility issues were identified in our review for ICS+LABA combination products for asthma. In fiscal 2012, 52.7% of all patients prescribed combination products had a diagnosis of asthma (both with and without a concurrent diagnosis of COPD); almost one-third (28%) of provincially-funded combination product users had a diagnosis of asthma with concurrent COPD. For patients under the age of 65 and without public or private coverage, access to asthma 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 asthma which is likely driven by ODB eligibility criteria. Our analysis found that asthma patients prescribed ICS+LABA tended to be over 65 years of age and lived in urban locations.

Use in Women

In Ontario in 2013, approximately 58% of patients with asthma were female.²⁷ Analysis of Ontario data showed that use of ICS+LABA was more common in females (62.5%), especially in users 18 years and older.

Use in Aboriginals

The prevalence of asthma in Aboriginals is higher than in non-Native populations. According to the 2005 Community Health Survey, the prevalence rate of asthma among Aboriginals was higher than in the non-Aboriginal population (11.7% and 8.3%, respectively).²⁸ A limitation of our pharmacoepidemiology

research is that we were unable to stratify our data into Aboriginals and non-Aboriginals, and therefore are unable to determine the use of ICS+LABA products in this population.

Reimbursement Options for Consideration

Key Considerations

Efficacy

- Our network meta-analysis found that adjustable or fixed dose combined ICS+LABA inhalers (any dose) had the greatest probability of decreasing the risk of moderate to severe exacerbations in patients with chronic asthma.
- Only 2 randomized controlled trials included in the review reported on symptom using the Asthma Control Test scale; neither study found a clinically relevant change in symptoms.

Safety and tolerability

- There were no significant differences in risk of cardiovascular disease (based on 3 RCTs) or cardiovascular-related mortality (based on 6 RCTs) across all treatment groups.
- Regular use of beta2-agonists (as monotherapy) in patients with asthma has shown to lead to increased asthma mortality.^{21;22} However, LABA in combination with ICS has not been shown to result in similar increased asthma mortality.

Accessibility

- In Ontario, ICS+LABAs are available on the ODB formulary as Limited Use for patients with asthma. As such, no accessibility issues for qualifying patients, including those aged 65 years and older, were identified in our review.
- For patients under the age of 65 and without public or private coverage, access to asthma medications including ICS+LABA.

Pharmacoeconomics

- *De novo Economic Evaluation:* The de novo economic evaluation found that the later LABA was introduced into therapy, the more cost-effective the treatment strategy became. Therefore, the optimal strategy considered was introducing LABA to patients when they were uncontrolled with high doses of ICS.
- *Budget Impact Analysis:* A policy of not funding either low dose ICS+LABA combination products or low and medium dose ICS+LABA combination products would generate costs savings ranging from \$0.4 to \$4M. However, if such policies lead to a reasonable proportion of patients (approximately 50%) uncontrolled on ICS moving to higher dose ICS+LABA combination products instead of higher dose ICS monotherapy, no savings will arise (increase in cost of \$2M).

Reimbursement Options

Reimbursement options for ICS+LABA for asthma (as well as ICS+LABA for COPD and LAMA for COPD) are presented in a companion report (see www.odprn.ca).

Conclusion

Final recommendations for the funding of ICS+LABA for asthma and COPD, and LAMAs for COPD through the publicly funded drug program in Ontario is available on the ODPRN website [“Final Reimbursement Options—Select drug therapies for treatment of chronic obstructive pulmonary disease (COPD) and asthma”].

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Appendix A: Health Equity Considerations for ICS+LABA for Asthma 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. A limitation of our pharmacoepidemiology research is that we were unable to stratify our data into Aboriginals and non-Aboriginals, and therefore are unable to determine the use of ICS+LABA products in this population
Age-related groups (e.g., children, youth, seniors, etc.)	Elderly: No restrictions for ICS+LABA use in the elderly were identified in the review. As asthma is a disease that largely impacts younger patients, high out-of-pocket costs were identified as a concern by our Qualitative Team.
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+LABAs) 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+LABAs 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.

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
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/hea/>)