

FINAL REPORT

Inhaled Corticosteroids (ICS) + long-acting beta-agonists (LABA) for treatment of chronic obstructive pulmonary disease (COPD)

Environmental Scan and Local/Historical Context

December 29, 2014

Executive Summary

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

There are four inhaled corticosteroids + long-acting beta-agonists (ICS+LABA) combination products available on the Canadian market: Advair (fluticasone + salmeterol), Symbicort (budesonide + formoterol), Zenhale (mometasone + formoterol) and BreoEllipta (fluticasone + vilanterol). 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. No generic formulation is available for any of these products. The cost of a one-month supply for these products ranges from approximately \$87 (Symbicort 6/200 2 inhalations twice daily) to \$146 (Advair 50/500 1 inhalation twice daily) (for the highest available dose of each product).

In Ontario, ICS+LABA products (i.e., fluticasone+salmeterol, budesonide+formoterol and mometasone+formoterol) 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. Nine of the 12 (75%) public drug programs in Canada list ICS+LABA combination products on a restricted basis (i.e., requiring prior authorization) for the treatment of COPD. In two provinces (Alberta and Manitoba), Advair and Symbicort are listed as general benefits. Various reimbursement schemes are used as funding models for ICS+LABA combination products in international jurisdictions including prior authorization, use of a preferred product or step-therapy.

Part B: Guidelines for the management of patients with COPD

Five guidelines were reviewed: Canadian Thoracic Society (2008), Global Initiative for Chronic Obstructive Lung Disease (2014), Institute for Clinical Systems Improvement (2013), NICE Guidance for COPD (2011) and American College of Physicians, American College of Chest Physicians, American Thoracic Society and the European Respiratory Society Guideline (2011). All guidelines recommend the use of ICS+LABA, either as a combination inhaler or as two separate inhalers, for the management of patients with COPD, in particular those patients with moderate to severe COPD.

Part C: Impact of different drug reimbursement schemes for ICS+LABAs for COPD

Despite these agents being restricted through the use of prior authorization or step therapy in both Canada and international jurisdictions, there is a paucity of literature assessing these reimbursement schemes for adherence or outcome measures (e.g., exacerbation rates, hospitalization). Based on the limited data available for cost-sharing options for inhaled medications used for COPD and asthma, increasing the amount that a patient is required to pay for a medication, either through higher deductibles or via co-insurance, may result in patients being less likely to initiate or continue treatment with an inhaled medication.

Part D: Rapid Review of Selected Topics

Delivery Devices: In a review of delivery devices, all devices (i.e., nebulizers, pressurized MDIs with or

without a spacer and DPIs) used for the delivery of bronchodilators and steroids were found to be equally efficacious. There were several factors that should be considered in selecting a device including: device/drug availability; patient age and ability to use the selected device correctly; drug administration time; and physician and patient preference. ICS+LABA combination products for the treatment of COPD (i.e., Advair Diskus, Symbicort and Breo Ellipta) are only available as a dry powder inhaler.

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Introduction

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.¹ Symptoms of COPD include breathlessness, excessive sputum production and a chronic cough.² 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.² Cigarette smoking is the principal underlying cause of COPD, and quitting has been associated with improved lung function, reduced chronic cough and a decreased mortality from COPD.^{1;3}

The worldwide prevalence of COPD is more than 10% among adults aged 40 years and older.⁴ In Ontario, there are 850,000 (11.8% of the population) diagnosed with COPD.⁵ 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, $p < 0.001$).⁶ However, approximately 60-85% of patients, mainly with mild to moderate disease, are thought to remain undiagnosed, as many patients may only seek treatment when symptoms are severe.⁷ Canadian data indicate similar findings for under diagnosis of COPD. Among Canadians aged 35 to 79 years, 4% reported having been diagnosed by a health professional with COPD, chronic bronchitis or emphysema.⁸ However, spirometry data collected by the Canadian Health Measures Survey (CHMS) revealed that 13% of Canadians aged 35 to 79 had an FEV1/FVC 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%.

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.⁹ In addition, approximately one in five patients with COPD (18.8%) were readmitted to acute inpatient care within 30 days of discharge.¹⁰ 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.⁵ COPD exacerbations are the major drivers for COPD morbidity and mortality, as well as most important component for direct healthcare costs.¹¹ Using a dynamic simulation model, the annual societal cost of COPD in Canada (cost, morbidity and mortality) was estimated at \$4.52 billion Canadian dollars in 2011.¹² COPD has a major impact on healthcare costs, lost productivity, absenteeism and presenteeism in the workplace.^{13;14} Patients with COPD also have a high symptom burden.¹⁵ In fact, patients with advanced COPD have symptoms that are comparable to those patients with cancer or congestive heart failure.¹⁶

Management strategies for patients with COPD include smoking cessation, drug therapy, 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. Drug therapy includes use of a bronchodilator to control symptoms with use of inhaled corticosteroid (ICS) in patients with more severe disease.¹ Bronchodilators are the cornerstone of treatment for patients with COPD and include beta2-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.

In Canada, there are four ICS+LABA combination products available. Two of these, namely fluticasone + salmeterol (Advair) and budesonide + formoterol (Symbicort), are indicated for both COPD and asthma. Fluticasone + vilanterol (Breo Ellipta) is only indicated for the treatment of COPD. Mometasone + formoterol (Zenhale) is currently licensed in Canada for the treatment of asthma.

The objectives of this report are:

- Part A: To summarize coverage of ICS+LABA combination products through public drug programs in Ontario and across Canada, as well as in select international jurisdictions
- Part B: To summarize the guidelines for management of patients with COPD, focusing on the role of ICS+LABA
- Part C: To review the evidence relating to the impact of different drug reimbursement schemes for ICS+LABA for COPD (e.g. cost sharing options) on patient access and/or utilization and costs
- Part D: To provide rapid reviews on selected topics, such as comparison of dry powder inhalers and metered dose inhalers

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

Availability and Costs of ICS+LABA combination products in Canada

There are currently four inhaled corticosteroids + long-acting beta-agonists (ICS+LABA) combination products available on the Canadian market: Advair (fluticasone + salmeterol), Symbicort (budesonide + formoterol), Zenhale (mometasone + formoterol) and BreoEllipta (fluticasone + vilanterol). 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.

Symbicort, BreoEllipta and Advair Diskus are available as a dry powder inhaler. Advair and Zenhale are available as a hydrofluoroalkane-propelled metered dose inhaler. There are currently no generic products available.

Exhibit 1 outlines the dosage forms and costs for the ICS+LABA combination products.

Exhibit 1: ICS+LABA combination products available in Canada

Drug Name	Brand name	Device	mcg/spray (package size)	DIN #	Available in Canada	Monthly cost * †	Dosing	Approved indications
Fluticasone + salmeterol	Advair Diskus	DPI	50 + 100 (60 DS)	02240835	1999	81.39	1 inhalation twice daily (COPD and asthma)	COPD Asthma (age ≥4 years)
			50 + 250 (60 DS)	02240836		97.43		
			50 + 500 (60 DS)	02240837		138.31		
	Advair	HFA-MDI	25 + 125 (120DS) 25 + 250 (120DS)	02245126 02245127	2001	97.43 138.31	2 inhalations twice daily (asthma)	Asthma (age ≥12 years)
Budesonide + formoterol	Symbicort	DPI	6 + 100 (120DS)	02245385	2002	63.80	1-2 inhalations once to twice daily (asthma); 2 inhalations twice daily (COPD)	COPD Asthma (age ≥12 years)
			6 + 200 (120DS)	02245386		82.90		
Mometasone + formoterol	Zenhale	HFA-MDI	5 + 50 (120DS)	02361744	2011	69.94	2 inhalations twice daily	Asthma (age ≥12 years)
			5 + 100 (120DS)	02361752		88.75		
			5 + 200 (120DS)	02361760		107.57		
Fluticasone furoate + vilanterol	Breo Ellipta	DPI	25 + 100 (14DS) 25 + 100 (30DS)	02408872	2013	59.08** 126.60**	One inhalation once daily	COPD

*Based on costs obtained from the Ontario Drug Benefit Formulary (accessed December 29, 2014)

**Based on costs obtained from McKesson (December 29, 2014)

†Based on recommended dosages in product monographs¹⁸⁻²⁰

Summary

- Three ICS+LABA combination products are currently indicated for the treatment of COPD: Advair Diskus, Symbicort and Breo Ellipta.
- The medications are packaged as a one-month supply (using the recommended doses for COPD).
- The monthly cost, at the recommended highest dose for COPD, ranges from \$82.90 (Symbicort 6/200 2 inhalations twice daily) to \$138.31 (Advair 50/500 1 inhalation twice daily).

Common Drug Review

The Common Drug Review (CDR) is a single process for reviewing new drugs and providing listing recommendations to participating publicly funded federal, provincial and territorial drug benefit plans in Canada; it was established in September 2003. Two products have been reviewed by the Common Drug Review: mometasone + formoterol (Zenhale) for the indication of asthma and fluticasone furoate + vilanterol (BreoEllipta) for the indication of COPD.^{21,22} Breo Ellipta was reviewed by CDR in August 2014 for the indication of COPD; it was recommended that this product be listed with criteria for patients with chronic obstructive pulmonary disease (see Appendix A for summary of CDEC recommendation). Fluticasone + salmeterol (Advair) and budesonide + formoterol (Symbicort) were available prior to 2003 and thus were not reviewed by the CDR.

Summary

- Advair and Symbicort were available prior to inception of the Common Drug Review; as such no review was conducted for these products.
- Zenhale was reviewed by the Common Drug Review 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.
- Breo Ellipta was reviewed by CDR in August 2014 for the indication of COPD; it was recommended that this product be listed with criteria for patients with chronic obstructive pulmonary disease.

ICS+LABA combination product listing in Ontario

Limited Use (LU)

Limited use (LU) drugs are drugs that have been deemed to have value in certain circumstances, although they may not be appropriate for general listing in the Formulary. Fluticasone + salmeterol (Advair products), mometasone + formoterol (Zenhale) and formoterol + budesonide (Symbicort) are available as limited use products for the treatment of patients with asthma. There are no LU criteria for patients with COPD nor is there any provision under the Exceptional Access Program for patients with COPD to access these combination drugs. It should be noted that the individual components for some of the agents are available on the Ontario Drug Benefit Formulary as a general benefit (inhaled corticosteroids) or as a limited use product (long-acting beta2-agonists)(see Appendix B for availability of the single entity ICS and LABA products, Appendix C for listing of LABA products in Canada, and Appendix D for restriction criteria for LABAs in Canada), and therefore it is likely that some patients are being treated with dual ICS and LABA therapy for COPD using these available products.

Committee to Evaluate Drugs:

The Committee to Evaluate Drugs (CED) is the Ministry of Health and Long-term care's independent expert advisory committee on drug-related issues. The CED reviewed and recommended listing for fluticasone + salmeterol (Advair), budesonide + formoterol (Symbicort) and mometasone + formoterol (Zenhale) for asthma.

The manufacturer of Advair submitted a request for review to CED for the indication of COPD in November 2003. At that time, Advair was listed as a Limited Use benefit for the treatment of asthma. After a review of the information presented by the manufacturer, the committee concluded that there was insufficient evidence to demonstrate additional clinical benefits achieved with fluticasone + salmeterol compared to salmeterol alone for patients with COPD and there is an increased risk of adverse events/long-term risks; a decision was made not to add the indication of COPD to the limited use criteria. A second review was requested by the manufacturer in February 2004. After reviewing the new information, the committee reiterated that there was insufficient evidence to demonstrate additional clinical benefit or value for money with fluticasone + salmeterol compared with standard COPD therapy such as a long-acting bronchodilator or regular use of a short-acting bronchodilator.

At the time of submission to the CED in June 2002, the manufacturer of Symbicort only requested review of this product for the indication of asthma, and not COPD. For drug products to be eligible for listing in the Formulary, a drug manufacturer must provide a complete submission for the specific indication.

Mometasone + formoterol (Zenhale) underwent a review in October 2011 by the CED for the indication of asthma only; the recommendation was that this product not be funded. Subsequent to the CED decision, an agreement was reached with the manufacturer and the product was listed on the ODB Formulary as a Limited Use Benefit for treatment of asthma.

Summary

- There are currently three ICS+LABA combination products available on the ODB formulary (Limited Use listing) for the treatment of asthma: fluticasone + salmeterol (Advair), budesonide + formoterol (Symbicort) and mometasone + formoterol (Zenhale).
- Neither fluticasone + salmeterol (Advair) nor budesonide + formoterol (Symbicort) are available on the ODB formulary for the treatment of COPD. After reviewing the evidence in 2004, the Committee to Evaluate Drugs (CED) recommended that Advair not be listed for treatment of COPD. No request was made by the manufacturer of Symbicort for review of this product in COPD.

Public Plan Listings in Canada

Part 1: Listing Status

In order to determine the listing of ICS+LABA combination products across Canada, the relevant webpages of the provincial drug formularies were searched (See Appendix E). In Canada, all public plans provide coverage for ICS+LABA combination products for eligible patients for COPD and asthma, except in Ontario, where these products are only funded for the indication of asthma. These products are available either as a general benefit or as a restricted benefit. The restricted benefit is passive (e.g., adjudicated at the pharmacy level) or enforced (e.g., prescriber is required to provide information, often in writing, regarding justification for use of ICS+LABA combination products). For those jurisdictions with restricted listing of these products, at least one of the products is listed for the management of COPD. Ontario is the only jurisdiction that does not list these combination products for management of COPD. A summary of the various listings (see Exhibit 2) is as follows:

- General benefits without restrictions: Alberta, Manitoba
- Restricted (passive): Ontario
- Restricted (enforced): British Columbia, Saskatchewan, Quebec, Nova Scotia, New Brunswick, Prince Edward Island, Newfoundland, NIHB/NT/NU, Yukon

Exhibit 2: 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

No=not listed;

Res=restricted listing - enforced

Pas= restricting listing – passive;

Ben=unrestricted listing

Restriction Criteria

In order for patients to be eligible for publically funded ICS+LABA combination products, various jurisdictions use restriction criteria, including severity of disease and/or previous use of other treatments.

Summary of the restriction criteria is found in Exhibit 3. See Appendix F for detailed criteria for each jurisdiction with restricted listing status.

Exhibit 3: Summary of Provincial Criteria for fluticasone + salmeterol (Advair) and budesonide + formoterol (Symbicort) (for restricted listing for COPD patients)

Restriction criteria for COPD patients	BC	SK	NB, NS, PEI, NL	NIHB, NT, NU	YK	QC
Inadequate response on optimal short-acting bronchodilator therapy	√*		√			
Practitioner exemptions	√*					
Concurrent or past use of tiotropium or LABA		√				
If no trial of SABA, then spirometric evidence of moderate to severe airflow obstruction and significant symptoms			√			
Combination tiotropium + ICS/LABA, if spirometric evidence of moderate to severe airflow obstruction, significant symptoms and evidence of one or more moderate-to-severe exacerbations per year for 2 years			√			
Moderate COPD if patient symptomatic after trial of LAMA and LABA; OR Severe COPD if patient symptomatic after trial of LAMA or LABA				√		
Treatment of moderate to severe COPD (with spirometry results)					√	
Severe COPD and control not achieved despite use of SABA, LABA and anticholinergic						√
Severe COPD who had one or more exacerbations in last year despite use of inhaled long-acting bronchodilator						√

Summary

- Nine of the 12 (75%) public drug programs in Canada list ICS+LABA combination products on a restricted basis for the treatment of COPD, requiring special authorization. In Ontario, there is no funding for these products for COPD. In two provinces (Alberta and Manitoba), Advair and Symbicort are listed as general benefits.
- Restriction criteria vary among the public drug plans including use of spirometry for confirmation of diagnosis in 5 plans, prior use of SABA and/or SAMA in 4 plans, and prior use of LAMA and/or LABA in 2 plans.

*Only Advair covered for patients with COPD

Part 2: Telephone Interview with Public Drug Program Representatives

A representative from each public drug program (except Quebec) was contacted to participate in a 30 minute telephone interview to gather further information about formulary listing of ICS+LABA for COPD (see Appendix G for interview questions). Exhibit 4 summarizes the information obtained in the interviews.

Exhibit 4: Summary of interviews with representative from public drug program

Province	Listing	Was there ever a change in listing?	What was the basis for listing/change in listing?
British Columbia	Restricted (enforced); practitioner exemptions for criteria (respirologists, allergists)	No	Listed as restricted based on cost and recommendation for use of ICS/LABA as second line agent in COPD
Alberta	General benefit	No	Individual components listed; less cost of ICS+LABA combination inhaler than 2 separate inhalers
Saskatchewan	Restricted (enforced)	2008: after publication of Canadian guidelines, criteria reviewed for Exception Drug Status Program Old criteria: "COPD: in patients who are uncontrolled on long-acting beta-2 agonists alone" New criteria: "COPD in patients where there has been concurrent or past use of tiotropium or a LABA (salmeterol or formoterol)"	Internal review after publication of Canadian COPD guidelines
Manitoba	General benefit	No	Internal review
Ontario	Restricted (passive) FOR ASTHMA ONLY	No	Not applicable
New Brunswick Nova Scotia Newfoundland PEI	Restricted (enforced)	Reviewed in 2008 with the following changes for criteria for special authorization: <ul style="list-style-type: none"> Patients with spirometric evidence of moderate to severe airflow obstruction will be eligible for coverage of one long-acting bronchodilator (e.g. tiotropium, salmeterol, or formoterol) without a trial of maximum doses of a short-acting bronchodilator. Patients with spirometric evidence of moderate to severe airflow obstruction and with more frequent exacerbations* will be eligible for coverage of both tiotropium and a long-acting beta2 agonist (LABA)/inhaled corticosteroid combination. 	Atlantic Common Drug Review (2008) based on publication of Canadian COPD guidelines The drug class ICS+LABA for COPD and asthma are currently undergoing review by the Atlantic Common Drug Review.

NIHB	Restricted (enforced)	<p>Reviewed in 2013:</p> <ul style="list-style-type: none"> • Symbicort now added as an indication for treatment of COPD • For moderate patients: require use of LABA + LAMA (either concurrently or consecutively); • For severe patients: require use of LABA or LAMA • Previously ipratropium or tiotropium AND SABA required for approval 	<ul style="list-style-type: none"> • Completion of CADTH Rapid Review in May 2013 • Symbicort not previously listed for COPD but were receiving requests from prescribers for COPD
Yukon	Restricted (enforced)	None	Listed as restricted based on cost and possible misdiagnosis of COPD

NA: not applicable

Summary

- Internal review of ICS+LABA listing for both COPD and asthma has recently been completed by the NIHB. As well, the Atlantic Common Drug Review is currently reviewing these products.
- Most public drug plans in Canada list ICS+LABA for COPD (and asthma) as medications requiring special authorization.

Selected International Jurisdictions

United States

As a measure to control ever-increasing costs associated with healthcare, the use of a preferred drug list (“formulary”) has been implemented in some jurisdictions. For example a preferred drug list is a list of medications that the provider will cover the cost for without the need to request a prior authorization. The preferred drugs are usually medications that are available generically or are the result of price negotiations between the pharmaceutical company and the provider. For example, in Kansas (Department of Health and Environment), the preferred ICS+LABA combination products are Advair and Dulera (mometasone + formoterol: Zenhale), whereas the non-preferred products are Breo Ellipta and Symbicort.²³

A tiered co-payment system is a combination of cost-sharing and a preferred drug list.²⁴ Three-tier structures commonly assign generic medications the lowest copay, formulary brand medications a somewhat higher copay, and non-formulary brand medications the highest copay. Three-tier copays provide consumers with more choice than in a closed formulary (where tier three drugs would not be covered at all) and attempt to reduce the number of prior authorizations that are needed for drug approval.²⁵ In a five-tier system, tier 1 includes preferred generic drugs, tier 2 non-preferred generic drugs, tier 3 preferred brand drugs, tier 4 non-preferred brand drugs and tier 5 specialty drugs (e.g., injectables) (see Appendix H for examples of copayments with tiered formulary systems). See Exhibit 5 for some sample listings of ICS+LABA combination products in the United States.

Exhibit 5: Listing of ICS+LABA Combination Products in selected plans in the United States

	Symbicort	Advair	Dulera (Zenhale)	Breo Ellipta
AETNA Preferred List (Chronic Medications: Asthma) (3-Tier system) (www.aetna.com)	Tier 2	Tier 3	Tier 2	Tier 3
Amerigroup Medication Formulary (Medicaid markets in Florida, Louisiana, Maryland, Nevada, New Jersey and Washington) (www.providers.amerigroup.com)	Preferred (step therapy: first tried on either Flovent, Serevent, Qvar)	Preferred (step therapy: first tried on either Flovent, Serevent, Qvar)	Preferred (step therapy: first tried on either Flovent, Serevent, Qvar)	Not listed
Blue Cross Blue Shield of South Carolina Preferred Drug List (www.southcarolinablues.com)	Preferred	Preferred	Preferred	Not listed
Blue Cross Blue Shield of Texas Standard Preferred Drug List (January 2014) (www.bcbstx.com)	Preferred	Preferred	Preferred	Preferred
Connecticut Medicaid Preferred Drug List (www.ctdssmap.com)	Preferred	Preferred	Preferred	Not listed
Idaho Medicaid Preferred Drug List (www.healthandwelfare.idaho.gov)	Non-preferred	Preferred (Special authorization) <u>Asthma</u> : Glucocorticoid/bronchodilator combinations will be approved for eligible participants with a documented diagnosis of persistent asthma and have tried and failed an inhaled glucocorticoid. <u>COPD</u> : Advair Diskus 250/50 will be approved for eligible participants with a diagnosis of Stage III or Stage IV COPD with repeated exacerbations and a failure of a long acting beta agonist inhaler (Foradil or Serevent).	Non-preferred	Not listed

Kaiser Permanente 2013 Medicare Part D Comprehensive Formulary (5-tier system) (www.healthy.kaiserpermanente.org)	Tier 4	Not listed	Tier 3	Not listed
Kentucky Preferred Drug List 2014 (www.kentucky.magellanmedicaid.com)	Preferred	Preferred	Preferred	Non-preferred
Oregon Fee-for-Service Enforceable Physical Health Preferred Drug List 2014 (http://www.oregon.gov/oha/healthplan/pages/tools_prov/pdl.aspx)	Preferred	Preferred	Not listed	Not listed
Texas Medicaid Preferred Drug List (http://www.txvendordrug.com/pdl/)	Preferred	Preferred	Preferred	Not listed
WellCare Comprehensive Formulary (Medicare Advantage Plans) (covers New York, Connecticut, Florida, Georgia, Hawaii and others) (5-tier system) (https://www.wellcare.com/medicare_formulary/new_york)	Non-preferred	Preferred (Tier 3)	Preferred (Tier 3)	Not listed
Wellmark Prior authorization/Step therapy (http://www.wellmark.com/HealthAndWellness/DrugInformation/PharmacyHome.aspx)	Preferred (Step therapy: Member must first try Asmanex or Qvar then maximum therapeutic doses of Dulera prior to approval. Treatment with single agent ICS therapy and Dulera must be considered for patients experiencing at least daily asthma symptoms prior to coverage of Advair)	Preferred (Step therapy: Member must first try Asmanex or Qvar then maximum therapeutic doses of Dulera prior to approval. Treatment with single agent ICS therapy and Dulera must be considered for patients experiencing at least daily asthma symptoms prior to coverage of Advair)	Preferred (Step therapy: Step Therapy. Member must first try Asmanex or Qvar.)	Not listed

Other Countries

Australia:

In Australia, the Pharmaceutical Benefits Scheme (PBS) restricts ICS+LABA combination products to patients with asthma and/or COPD, depending on the dosage form of the product.²⁶ See Exhibit 6 for ICS+LABA combination products available under PBS for treatment of COPD.

Exhibit 6: ICS+LABA combination products for COPD (Australia)

Product	Dosage form	Criteria (COPD)
Budesonide+eformoterol (Symbicort Turbuhaler)	400/12 mcg	Patient must have a forced expiratory volume in 1 second (FEV1) less than 50% of predicted normal prior to therapy, AND Patient must have a history of repeated exacerbations with significant symptoms despite regular beta-2 agonist bronchodilator therapy, AND The treatment must be for symptomatic treatment.
Fluticasone+salmeterol (Seretide) ²⁷	500/50 mcg 250/25 mcg	
Budesonide + eformoterol (Symbicort Rapihaler)	200/6 mcg	Patient must have a forced expiratory volume in 1 second (FEV1) less than 50% of predicted normal prior to therapy, AND Patient must have a history of repeated exacerbations with significant symptoms despite regular beta-2 agonist bronchodilator therapy

Scotland:

In Scotland, the higher dose of Seretide (Advair) 500/50mcg is not recommended for COPD, although it does fund Seretide 250/50mcg and Symbicort.²⁸ See Exhibit 7 for advice for ICS+LABA combination products in Scotland.

Exhibit 7: ICS+LABA combination products for COPD (Scotland)

Product	Dosage form	Advice/criteria
Fluticasone + salmeterol (Seretide Accuhaler)	50/500 mcg	<p>Not recommended for symptomatic treatment of patients with COPD with FEV1 50% to <60% predicted and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.</p> <p>While there were improvements in lung function tests and reductions in moderate exacerbations with the fluticasone/salmeterol combination compared to placebo and to salmeterol alone, there were no significant differences in mortality rates over 3 years. In addition, the manufacturer did not present a sufficiently robust economic case to gain acceptance by SMC. (2009)</p>
Fluticasone + salmeterol (Seretide Accuhaler)	250/25	<p>Accepted for use for treatment of patients with severe COPD.</p> <p>The individual components have been available for many years and the combination product offers ease of administration and additional convenience. The combination appears to improve lung function to a greater extent than either of the individual constituents given alone. Comparative data with other combination products are limited at the present time. (2003)</p>
Budesonide +formoterol (Symbicort Turbuhaler)	NA	<p>Accepted for use for treatment of patients with severe COPD (FEV1 <50%), history of repeated exacerbations who have significant symptoms despite regular therapy with long-acting bronchodilators.</p> <p>The individual components have been available for many years and the combination product offers ease of administration and additional convenience. The combination appears to improve lung function to a greater extent than either of the individual constituents given alone. Comparative data with other combination products are limited at the present time. (2004)</p>

Summary

- In the United States, most health plans list Advair and Symbicort as preferred drugs on the formularies. Some drug plans list either Advair OR Symbicort as their preferred ICS+LABA combination product for treatment of asthma and COPD.
- In Australia, ICS+LABA combination products are funded for patients with moderate to severe COPD.

Part B: Guidelines for the management of patients with COPD

Various guidelines, both Canadian and international guidelines, have been published for the management of patients with COPD. A summary of these guidelines is below.

Canadian Guidelines

Canadian Thoracic Society (2008)²⁹

The Canadian Thoracic Society's classification of severity is based on symptoms and disability (see Exhibit 8). The number of annual exacerbations is also used in classifying patients according to their COPD severity.

Exhibit 8: Canadian Thoracic Society COPD classification

COPD stage	Symptoms	Exacerbations
Mild	Shortness of breath from COPD when hurrying on the level or walking up a slight hill (MRC 2)	NA
Moderate	Shortness of breath from COPD causing the patient to stop after walking approximately 100m (or after a few minutes) on the level (MRC 3 to 4)	Average of <1 per year
Severe	Shortness of breath from COPD resulting in the patient being too breathless to leave the house, breathless when dressing or undressing (MRC 5), or the presence of chronic respiratory failure or clinical signs of right heart failure	Frequent exacerbations ≥ 1 per year

MRC: Medical Research Council (see Appendix I)

The Canadian Thoracic Society's guidelines for the management of patients with COPD, based on their COPD stage, are as follows:

- Short-acting bronchodilators (both anticholinergics and beta2-agonists, either as monotherapy or as combination therapy) are used on an as needed basis for initial mild disease.
- Long-acting bronchodilators (i.e., LABAs and long-acting anticholinergics) are added on in patients with persistent disability.
- Patients with moderate to severe COPD with persistent symptoms but infrequent exacerbations, will often require a long-acting anticholinergic and a LABA; lower dose ICS+LABA could be substituted for LABA to maximize bronchodilation in patients with persistent dyspnea. For patients with moderate to severe COPD with persistent symptoms and a history of exacerbations, a combination of LAMA plus a LABA and ICS therapy is recommended.
- Patients with severe COPD require triple inhaled therapy (tiotropium + LABA + inhaled

corticosteroid) with theophylline as indicated.

International Guidelines

Global Initiative for Chronic Obstructive Lung Disease (2014)³⁰

Evidence-based guidelines for COPD diagnosis, management and prevention were recently updated by Global Initiative for Chronic Obstructive Lung Disease (GOLD). Although previous versions of GOLD treatment recommendations were based on spirometry (i.e., lung function) only, the most recent edition uses other factors such as number of exacerbations and patient's symptoms, to classify patients (see Appendix J). Treatment strategies for patients with COPD are found in Exhibit 9.

Exhibit 9: Global Initiative for Chronic Obstructive Lung Disease (GOLD): Treatment of Patients with COPD (Global Initiative for Chronic Obstructive Lung Disease)³⁰

COPD Severity	Recommended first choice	Alternative choice
Group A (low risk, less symptoms)	SABA or SAMA	LAMA or LABA or SABA + SAMA
Group B (low risk, more symptoms)	LABA or LAMA	LAMA + LABA
Severe (high risk, less symptoms)	ICS + LABA or LAMA	LAMA + LABA Or LAMA + PDE4 inhibitor Or LABA + PDE4 inhibitor
Very severe (high risk, more symptoms)	ICS + LABA and/or LAMA	ICS + LABA + LAMA or ICS + LABA + PDE4 inhibitor or LAMA + LABA or LAMA + PDE4 inhibitor

SABA: short-acting beta2-agonist

SAMA: short-acting muscarinic antagonist

LABA: long-acting beta2-agonist

LAMA: long-acting muscarinic antagonist

ICS: inhaled corticosteroid

PDE4: phosphodiesterase-4

Institute for Clinical Systems Improvement (2013)³¹

An evidence-based guideline for people with symptoms of stable COPD, as well as acute exacerbations of COPD in the outpatient setting was published in 2013 by ICSI. Recommendations for treatment strategies (see Exhibit 10) are based on COPD severity as predicted by lung function (using definitions as proposed by GOLD).

Exhibit 10: Institute for Clinical Systems Improvement Guidelines for Management of COPD³²

COPD Severity	FEV1% Predicted	Add:
Mild	≥80%	<ul style="list-style-type: none"> Short-acting bronchodilators as needed for symptoms
Moderate	50-79%	<ul style="list-style-type: none"> Daily long-acting bronchodilators (LABA or LAMA) Pulmonary rehabilitation Inhaled corticosteroids are indicated if hospitalized for frequent COPD exacerbations Consider adding a PDE4 inhibitor
Severe	30-49%	<ul style="list-style-type: none"> Daily long-acting bronchodilators as above plus inhaled corticosteroids to reduce exacerbations Oral steroid bursts for exacerbations
Very severe	<30% or <50% plus chronic respiratory failure	<ul style="list-style-type: none"> Combination therapy as above Oral steroids as needed

NICE Guidance for COPD (2011)³³

The pharmacotherapy guidelines for COPD are as follows:

- In people with stable COPD who remain breathless or have exacerbations despite use of short-acting bronchodilators as required, offer the following as maintenance therapy:
 - If FEV1 ≥50% predicted: either long-acting beta2-agonist (LABA) or long-acting anticholinergic agent
 - If FEV1 <50% predicted: either LABA with an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic agent
- Offer long-acting anticholinergic agent in addition to LABA + ICS in people who remain breathless or have exacerbations despite taking LABA+ICS, irrespective of their FEV1.

American College of Physicians, American College of Chest Physicians, American Thoracic Society and the European Respiratory Society have endorsed the following recommendations (2011)³⁴

- Recommendation 1: Spirometry should be obtained to diagnose airflow obstruction in patients with respiratory symptoms.
- Recommendation 2: For stable COPD patients with respiratory symptoms and FEV1 between 60 and 80% predicted, treatment with inhaled bronchodilators may be used.
- Recommendation 3: For stable COPD patients with respiratory symptoms and FEV1 <60% predicted, treatment with inhaled bronchodilators is recommended.
- Recommendation 4: Monotherapy using either long-acting inhaled anticholinergics or long-acting inhaled beta-agonists for symptomatic patients with COPD and FEV1<60% predicted.
- Recommendation 5: Combination inhaled therapies (long-acting inhaled anticholinergics, long-acting inhaled beta-agonists or inhaled corticosteroids) for symptomatic patients with stable COPD and FEV1 <60% predicted.
- Recommendation 6: Pulmonary rehabilitation for symptomatic patients with an FEV1<50% predicted.
- Recommendation 7: Continuous oxygen therapy in patients with COPD who have severe resting hypoxemia.

Guidelines for use of ICS/LABA combination products

The combination of ICS + LABA (either as a single inhaler or as two separate inhalers) is recommended in all guidelines for patients with symptomatic disease. However, there is some variability as to when ICS+LABA therapy is initially recommended, based on severity of disease. Guidelines grade severity of disease on FEV1 measurements, symptoms and/or number of exacerbations per year. A comparison of the various guidelines, what stage of disease ICS+LABA is initially recommended and what other therapy (if any) is recommended as alternatives to ICS+LABA, is shown in Exhibit 11.

Exhibit 11: Comparison of guidelines for initial treatment of ICS+LABA

Guideline	Stage of disease ICS+LABA first recommended	Combination therapy
American College of Physicians, American College of Chest Physicians, American Thoracic Society and the European Respiratory Society	Symptomatic patients with stable COPD and FEV1 <60% predicted	Combination inhaled therapies (LAMA, LABA or ICS)
NICE Guidance for COPD	FEV1 <50% predicted	ICS+LABA (combination inhaler) or LAMA
Global Initiative for Chronic Obstructive Lung Disease (GOLD)	Severe (high risk, less symptoms)	ICS + LABA or LAMA
Institute for Clinical Systems Improvement	Severe (FEV1: 30-49% predicted)	LABA or LAMA plus ICS to reduce exacerbations
Canadian Thoracic Society	Moderate	LAMA and/or LABA (+/- ICS) plus short-acting bronchodilator prn

Summary

- All guidelines recommend the use of ICS+LABA, either as a combination inhaler or as two separate inhalers, for the management of patients with COPD, in particular among those patients with moderate to severe COPD.

Part C: Impact of different drug reimbursement schemes for ICS+LABA combination products for COPD

Methods

A literature search was conducted in Pubmed using the terms: glucocorticoids AND bronchodilator agents AND chronic obstructive pulmonary disease AND health services accessibility OR treatment outcome OR drug utilization review OR managed care programs OR insurance pharmaceutical services. Bibliographies of identified articles were scanned for additional relevant articles.

Results

Cost-sharing programs for patients with COPD

Cost sharing programs are used in many countries for several reasons including the promotion of appropriate utilization of health care services and the reduction for the demand for health care services.³⁵ At least three different types of cost sharing have been used in various plans including deductibles, co-insurance and co-payments.³⁵

The impact of fixed co-payment and income-based cost-sharing policies were assessed on the use of inhaled medications (for both asthma and COPD) in British Columbia.³⁶ Before January 2002, BC residents aged 65 and older received full coverage for all prescription costs, except for dispensing fees. In January 2002, a fixed prescription copayment policy was implemented for those 65 years and older. Finally in May 2003, the copayment for older individuals was replaced with a 25% coinsurance plus income-based deductible policy. In a study to assess the impact of cost-sharing policies on use of inhaled medications, data was extracted for all patients 65 years and older from linkable prescription, physician billing, hospitalization and mortality records from the BC Ministry of Health Services. Patients with new diagnoses of asthma or COPD were 25% (95% CI, 14-31%) less likely to initiate treatment with inhaled steroids when covered by the copayment or coinsurance plus deductible policies than when they had full coverage. In addition, chronic users of inhaled steroids were 47% (95% CI, 40-55%) more likely to cease treatment when they were covered by the copayment policy and 22% (95% CI, 15-29%) more likely to discontinue treatment when covered by the coinsurance plus deductible policy than when they had full coverage.

In a subsequent analysis, increases in emergency admissions and physician visits due to COPD, asthma or emphysema were observed to be greater in the income-based deductible policy than the fixed copayment policy coverage.³⁷ The study population included 37,320 users of long-term inhaled medications from the BC population of 576,000 persons over the age of 64. During the income-based deductible policy period but not the fixed copay period, emergency hospitalizations increased 41% (95% CI for adjusted rate ratio, 1.24-1.60) in patients 65 years and older. There was also a significant increase in physician visits of 3% (95% CI for adjusted RR, 1.01-1.05). No significant increases were observed

during the fixed copay period.

Other reimbursement options

No information was found that specifically addressed the issue of use of prior authorization as a reimbursement option for ICS+LABA for patients with COPD. However, there is limited information available regarding the use of a prior authorization process for patients with asthma. A retrospective cohort study from Quebec assessed the impact of a prior authorization process for reimbursement of combination drugs (budesonide+ formoterol and fluticasone + salmeterol) by measuring the rate of asthma-related emergency department visits and hospitalizations.³⁸ This study was conducted in Quebec where a prior authorization process was introduced in 2003 to limit the nonoptimal use of medications combining ICS plus long-acting bronchodilators. Two periods were assessed in the study: the preprocess phase and the post-process phase. The risk of an asthma-related first hospitalization or emergency department visit remained unchanged in the 2 periods in both publicly insured (adjusted HR, 0.95 (95% CI, 0.88-1.03), and the privately insured (adjusted HR, 1.03 (95% CI, 0.96-1.03). The change in risk between the preprocess and post-process periods was not significantly different between insurance groups. The authors concluded that the prior authorization process had no apparent effect on asthma-related hospitalization or emergency department visit.

Summary

- Based on the limited data available for cost-sharing options for inhaled medications used for COPD and asthma, increasing the amount that a patient is required to pay for a medication, either through higher deductibles or via co-insurance, may result in patients being less likely to initiate or continue treatment with an inhaled medication.
- One study from Quebec suggests that the implementation of a prior authorization process for ICS+LABA combination products does not lead to increased rates of asthma-related hospitalization or emergency department visits. However, there are no studies that have assessed outcomes in patients with COPD after implementation of a prior authorization process.

Part D: Rapid Review of Selected Topics

Methods of Drug Delivery: MDIs and DPIs

Inhaled aerosols have revolutionized the delivery of medication to the airways. Inhaled aerosols allow selective treatment of the lungs directly by achieving high drug concentrations in the airways and minimizing systemic adverse effects.³⁹ However, specific inhalation techniques are needed for proper use of each of the devices; incorrect technique can result in potentially reduced efficacy. Two common modes of inhalational delivery include the pressurized metered-dose inhaler and the breath-actuated dry powder inhalers. Nebulized delivery of inhaled medication is another mode of delivery; however, for the purposes of this review, these will not be discussed as there are no ICS+LABA combination products available via this route.

In Canada, for ICS+LABA combination products, Advair Diskus, Symbicort and Breo Ellipta are all available as DPI devices. Advair and Zenhale are available as MDI; however, it should be noted that these products are not officially indicated for COPD in Canada.

Metered-dose inhaler (MDI)

Pressurized multi-dose inhalers (MDIs) are pressurized aerosol canisters that contain medication either in solution or suspension in a liquefied gas propellant.⁴⁰ Hydrofluoro-alkane (HFA) is the propellant used in most MDIs. MDIs are compact and portable and provide consistent dosing and rapid delivery. However, most MDIs do not have dose counters, so it is difficult for patients to tell how much drug is remaining.⁴¹

Difficulties using MDIs are frequently encountered. In a meta-analysis of 24 studies of MDI use, 77% of patients with asthma and COPD made at least one error during use of the MDI.⁴² In patients with COPD, inadequate hand-breath coordination, poor fine motor control and hand or finger muscle weakness may result in the incorrect use of an MDI.⁴³ In the elderly, additional physical and cognitive changes may contribute to the challenges faced when using handheld inhalers.⁴⁴

Spacers

A spacer is a generic term that refers to simple open tubes that are placed on the mouthpiece of a metered dose inhaler to extend it away from the mouth of the patient. Compared with an MDI alone, spacers minimize coordination difficulties and reduce oropharyngeal deposition.⁴⁵ However, in patients able to use an MDI correctly, spacers do not improve the clinical effect of the medication administered.⁴⁵ One of the main disadvantages of holding chambers is their bulkiness. Note that spacers cannot be used with DPIs.

Spacers have consisted of manufactured and homemade devices such as plastic bottles, corrugated ventilation tubing, toilet tissue cores etc. Valved holding chambers are manufactured devices that have one-way valves that do not allow the patient to exhale into the device. By acting as an aerosol reservoir, these devices slow the aerosol velocity and increase transit time and distance between the MDI actuator and the patient's mouth, and allow aerosol particle size to decrease. As a result, the proportion of the aerosol reaching the lung periphery increases. As well, since spacers trap larger particles, only a small

fraction of the total drug dose is deposited in the oropharynx, thereby reducing side effects such as throat irritation, dysphonia and oral candidiasis.⁴⁶

In terms of bronchodilation, some studies suggest that spacers do not confer any additional benefit when the MDIs alone are correctly used; in contrast other trials show that, compared to MDI alone, spacers do enhance bronchodilation.⁴⁷ The difference in the results may have been due to inclusion of patients with poor MDI technique.⁴⁶ As well, in vitro and in vivo studies comparing various spacers/holding chambers with the same MDI have demonstrated a two- to six-fold variation in the respirable dose emitted from the devices and two- to five-fold difference in systemic availability of the drug.^{48;49}

In patients who require high doses of beclomethasone dipropionate, the addition of a spacer to the MDI markedly reduced the incidence of oral candidiasis, and also resulted in a continuing trend of improvement in airflow obstruction over 3-6 months, which did not occur in patients using the MDI alone.⁴⁶

Many of the original studies with spacers were done with CFC-MDIs. The interaction of HFA-driven inhalers with spacers is complicated by differences in spacer characteristics and formulations within the inhaler, as well as by the development of electrostatic charges. In one study, the inhalation of beclomethasone dipropionate extra-fine particles delivered via an HFA-driven inhaler with an attached spacer resulted in a high lung deposition and marked decrease in oropharyngeal deposition compared with delivery of the same formulation via the HFA-driven inhaler alone.⁵⁰ Overall, the addition of spacers to HFA-driven inhalers reduces the incidence of local adverse effects and improves drug delivery to the lungs, similar to CFC-MDIs.

Since improper MDI technique is common, a spacer device can help optimize the delivery of drug from a MDI and is highly recommended, especially with inhaled steroid therapy.^{45 46} It should be used if a patient is unable to properly use an MDI alone or if oropharyngeal or systemic effects are a problem. For elderly patients with COPD who require the use of an MDI, the addition of a spacer is recommended to optimize the delivery of drug from a MDI.⁵¹ However, it should be noted that ICS+LABA combination products approved for use in patients with COPD are only available in dry powder inhaler format.

Dry powder inhaler (DPI)

A dry powder inhaler is a breath actuated device that delivers the drug in the form of particles contained in a capsule or blister that is punctured prior to use. These devices are small and portable and provide rapid delivery, similar to an MDI. Since these inhalers are breath-activated, it eliminates the need to synchronize inhalation with actuation. However, DPIs require an adequate inspiratory flow rate (ideally about 60L/min, although most devices only require an inhalation flow rate of about 27 L/min) for drug delivery, as there is no propellant.^{40;52;53} In contrast to MDIs, multi-dose DPIs incorporate dose counters.⁴¹

DPIs must be loaded before each inhalation, and this may require opening blister packs that contain the

medication capsules.⁵⁴ There is a potential to use the DPI device incorrectly, including failure to exhale before actuation and failure to hold the breath after inhaling.⁴⁰ In one study, the error rate associated with DPI technique increased with age and with the severity of airway obstruction.⁵⁵ For example, with the Turbuhaler, the error rate was 25.4% in subjects less than 60 years of age and 46% in those over the age of 60 ($p < 0.05$, OR 0.4; 95% CI 0.18-0.90). As well, error rates were 25% with normal lung function and 64% with severe obstruction including those patients with COPD ($p < 0.05$).

Patients with COPD who are experiencing an exacerbation, low inspiratory flow rates may limit the use of DPIs. However, most patients who can perform adequate spirometry can usually generate a sufficient peak inspiratory flow rate to operate most DPIs.⁵⁶ For example, Turbuhaler DPI, which showed the greatest dependence on flow rate in simulation studies, has been successfully used in patients with COPD worsening.⁵⁶

Summary

In a systematic review of delivery devices, all devices (i.e., nebulizers, pressurized MDIs with or without a spacer and DPIs) used for the delivery of bronchodilators and steroids were found to be equally efficacious.³⁹ It should be noted that once patients are correctly taught the technique for using an inhaler, there is no difference in patients' ability to use DPI or MDIs.⁴² There were several factors that should be considered in selecting a device including: device/drug availability; patient age and ability to use the selected device correctly; drug administration time and physician and patient preference.⁵⁴

Health Canada Alerts and Warnings

- No Health Canada advisories have been issued for Symbicort, Zenhale or Breo Ellipta.
- For Advair, a potential drug interaction between fluticasone propionate and ritonavir, leading to increased plasma concentrations of corticosteroid, was highlighted in an advisory in 2004. (<http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2004/14261a-eng.php>)
- For LABAs (including salmeterol and formoterol) as a single inhaler for the treatment of asthma, an advisory was issued in 2005 regarding increased risk of asthma-related death in patients using these products. (<http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2005/13442a-eng.php>)

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

Although Symbicort and Advair are indicated for the management of patients with asthma and/or COPD, there is some suggestion that these products are used off-label for other indications such as post-infectious cough or bronchiectasis. For example, in a recent review by the Australian Drug Utilisation SubCommittee of the Pharmaceutical Benefits Advisory Committee of budesonide+formoterol (Symbicort) for COPD, the committee noted that there was a trend towards more initiations in winter compared to summer months. The Committee considered that this may indicate some use of the product outside of use for COPD, for example respiratory tract infections and cough.⁵⁷ As well, references in the lay literature indicate that these products are used off-label for other indications, in particular use in postinfectious cough. (<http://www.kevinmd.com/blog/2012/06/advair-treat-postinfectious-cough.html>)

However, despite some suggestion that these products are used for other indications other than asthma and COPD, limited information is available in the published peer-reviewed literature. In a Phase II trial, the use of ICS+LABA combination product was evaluated for patients with persistent cough after pulmonary resection. This was a prospective, unblinded, non-randomized trial that enrolled 21 patients ICS+LABA combination product for their chronic cough. Cough was assessed using a visual analog scale. Prior to start of inhaled treatment the median score on the VAS was 4 (range 3-8). Following 2 weeks of treatment, the median grade of cough decreased to 1 (range 0-4).⁵⁸ A randomized, double-blind clinical 12-month trial evaluated formoterol-budesonide (18/640mcg daily) treatment or budesonide alone (1600 mcg daily) in 40 patients with non-cystic fibrosis bronchiectasis.⁵⁹ Patients receiving combined therapy (vs. budesonide alone) showed statistically and clinically significant improvement of degree of dyspnea (transition dyspnea index, 1.30 vs 0.1; p=0.001) as well as an increase in the percentage of cough-free days (15.3% vs 3%, p=0.02). No statistically significant differences were observed for the treatment groups for number of exacerbations, hospitalization or number of requested antibiotics or oral steroids.

It should be noted that inhaled corticosteroids alone (without LABA) have been used in some of the conditions leading to chronic cough. Clinical guidelines recommend empirical ICS treatment for cough variant asthma, non-asthmatic eosinophilic bronchitis, chronic bronchitis, post-infectious cough and for non-specific and refractory cough.⁶⁰⁻⁶² However, the efficacy of ICS is contentious, with RCTs leading to conflicting results. In a systematic review and meta-analysis evaluating inhaled corticosteroids for non-specific chronic cough, the authors concluded that the clinical impact of using high dose ICS is unlikely to be beneficial.⁶³ Another systematic review and meta-analysis evaluated inhaled corticosteroids for subacute and chronic cough in adults. The authors stated that the studies were highly heterogeneous and results were inconsistent, and noted that a trial of ICS should only be considered in adults after thorough work-up including chest X-ray and consideration of spirometry and other investigations.⁶⁴

Summary

Published peer-reviewed literature does not support the use of ICS+LABA for non-approved indications, including cough (in particular post-infectious) and bronchiectasis.

Discussion

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

Availability in Canada

- There are four inhaled corticosteroids + long-acting beta-agonists (ICS+LABA) combination products available on the Canadian market: Advair (fluticasone + salmeterol), Symbicort (budesonide + formoterol), Zenhale (mometasone + formoterol) and BreoEllipta (fluticasone + vilanterol). 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.
- No generic formulation is available for any of these products.
- The cost of a one-month supply for these products ranges from approximately \$87 (Symbicort 6/200 2 inhalations twice daily) to \$146 (Advair 50/500 1 inhalation twice daily) (for the highest available dose of each product).

Public Plan Listing in Ontario

- In Ontario, ICS+LABA products are available on the ODB formulary for the treatment of asthma only under the Limited Use program.
 - Advair for the treatment of COPD was reviewed by the Committee to Evaluate Drugs (CED) in 2003 and 2004. CED recommended that this product NOT be listed for the treatment of COPD as they concluded that there was insufficient evidence to demonstrate additional clinical benefit or value for money with fluticasone + salmeterol compared with standard COPD therapy such as a long-acting bronchodilator or regular use of a short-acting bronchodilator.
 - Mometasone + formoterol (Zenhale) is listed under the LU program for the treatment of asthma only. It is not indicated for COPD, and therefore the manufacturer did not request review of this product for the COPD indication.
 - It should be noted that the manufacturer of Symbicort did not request review of this product for the treatment of COPD.

Public Plan Listing in Canada

- ICS+LABAs are available as benefits on public drug programs across Canada.
 - General benefits without restrictions: Alberta, Manitoba
 - Restricted (passive): Ontario (for asthma only)
 - Restricted (enforced): British Columbia, Alberta, Saskatchewan, Quebec, Nova Scotia, New Brunswick, Prince Edward Island, Newfoundland, NIHB/NT/NU, Yukon
- For those jurisdictions with restricted listing of these products, at least one of the products is listed for the management of COPD.
- Restriction criteria for ICS+LABA combination products include:

- Prior use and inadequate response on short-acting bronchodilator therapy (5 plans)
- Spirometric evidence of moderate to severe COPD with symptoms (5 plans)
- Concurrent or past use of tiotropium or LABA (1 plan)
- Patient with moderate or severe COPD is symptomatic despite use of LAMA and LABA (1 plan)
- Patient with severe COPD and symptomatic despite use of SABA, LABA and LAMA OR had one or more exacerbations in last year despite use of inhaled long-acting bronchodilator (1 plan)

Selected International Jurisdictions

- ICS+LABA combination products were available as preferred drugs (i.e., on formulary) for both asthma and COPD through all surveyed third-party payers, including managed care organizations.
- The preferred drugs are usually medications that are available generically or are the result of price negotiations between the pharmaceutical company and the provider. For example, in Kansas (Department of Health and Environment), the preferred ICS+LABA combination products are Advair and Dulera (mometasone + formoterol: Zenhale), whereas the non-preferred products are Breo Ellipta and Symbicort.
- Some third-party payers use step therapy (e.g., use of Flovent, Serevent, Qvar before ICS+LABA combination product) or prior authorization for ICS+LABA combination products.
- In Australia, the Pharmaceutical Benefits Scheme restricts ICS+LABA combination products to patients with asthma and/or COPD, depending on the dosage form of the product.

Part B: Guidelines for the management of patients with COPD

- Five guidelines were reviewed: Canadian Thoracic Society (2008), Global Initiative for Chronic Obstructive Lung Disease (2014), Institute for Clinical Systems Improvement (2013), NICE Guidance for COPD (2011) and American College of Physicians, American College of Chest Physicians, American Thoracic Society and the European Respiratory Society (2011).
- All guidelines recommend the use of ICS+LABA, either as a combination inhaler or as two separate inhalers, for the management of patients with COPD, in particular those patients with moderate to severe COPD. Other options for the management of patients with moderate to severe COPD include LAMAs, LABA + LAMAs or triple therapy with LAMA+LABA+ICS.

Part C: Impact of different drug reimbursement schemes for ICS+LABAs for COPD

- Despite these agents being restricted through the use of prior authorization or step therapy in both Canada and international jurisdictions, there is a lack of literature assessing these reimbursement schemes for adherence or outcome measures (e.g., exacerbation rates, hospitalization).
- Based on the limited data available for cost-sharing options for inhaled medications used for COPD and asthma, increasing the amount that a patient is required to pay for a medication, either through higher deductibles or via co-insurance, may result in patients less likely to initiate or continue treatment with an inhaled medication.

- One study from Quebec suggests that the implementation of a prior authorization process for ICS+LABA combination products does not lead to increased rates of asthma-related hospitalization or emergency department visits. However, there are no studies that have assessed outcomes in patients with COPD after implementation of a prior authorization process.

Part D: Rapid Reviews of Selected Topics

- Delivery devices:
 - In a systematic review of delivery devices, all devices (i.e., nebulizers, pressurized MDIs with or without a spacer and DPIs) used for the delivery of bronchodilators and steroids were found to be equally efficacious.
 - There were several factors that should be considered in selecting a device including: device/drug availability; patient age and ability to use the selected device correctly; drug administration time and physician and patient preference.
 - ICS+LABA combination products for the treatment of COPD (i.e., Advair Diskus, Symbicort and Breo Ellipta) are only available as a dry powder inhaler.
- Use of ICS+LABA combination products for non-approved indications:
 - Published peer-reviewed literature does not support the use of ICS+LABA for non-approved indications, including cough (in particular post-infectious) and bronchiectasis

Health Equity

Across Canada, at least one of the ICS+LABA combination products is available in every jurisdiction, with the exception of Ontario, for the treatment of patients with COPD. In Ontario, ICS+LABA combination products are not available for treatment of patients with COPD; these products are available on the ODB formulary as Limited Use products for the treatment of asthma. It should be noted the separate components are available on the ODB formulary either as general listing (inhaled corticosteroids) or limited use product (salmeterol).

Conclusion

ICS+LABA combination products are available in Canada for the treatment of asthma and/or COPD. All guidelines for the management of patients with COPD recommend the use of ICS+LABA, either as a combination inhaler or as two separate inhalers, for the management of patients with COPD, in particular those patients with moderate to severe COPD.

In Canada, all public drug programs fund at least one ICS+LABA combination product for the treatment of COPD, with the exception of Ontario. In Ontario, ICS+LABA products are available on the ODB formulary only for the treatment of asthma under the Limited Use program. Most public drug programs in Canada require special authorization prior to funding of these drugs for patients with COPD or asthma. Many international jurisdictions use step therapy (e.g., use of inhaled corticosteroid alone or LABA alone, before ICS+LABA combination product) or prior authorization for ICS+LABA combination products. However, there is a lack of literature assessing these reimbursement schemes for adherence

or outcome measures (e.g., exacerbation rates, hospitalization).

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Appendix A: CDEC Recommendation for fluticasone furoate/vilanterol (*Breo Ellipta*)

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that fluticasone furoate/vilanterol (FF/V) be listed for the long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and to reduce exacerbations of COPD in patients with a history of exacerbations, if the following clinical criteria are met:

Clinical Criteria:

- Moderate to severe COPD as defined by spirometry.
- Inadequate response to a long-acting bronchodilator (long-acting beta-2 agonist [LABA]/long-acting muscarinic antagonist [LAMA]) or experiencing exacerbations more than once per year while on a long-acting bronchodilator.

Reasons for the Recommendation:

1. Five randomized controlled trials (RCTs) demonstrated that FF/V was similar to tiotropium (TIO) and fluticasone propionate/salmeterol (FP/S) for improving forced expiratory volume in one second (FEV1) in patients with moderate to severe COPD.
2. At the submitted price (100 mcg/25 mcg once daily; \$xxxx per day), FF/V is less costly than FP/S (250 mcg/50 mcg to 500 mcg/50 mcg twice daily; \$3.25 to \$4.61 per day) and xxxx budesonide/formoterol (400 mcg/12 mcg twice daily; \$2.76 per day).

Of Note:

CDEC noted that the listing status of LABA/inhaled corticosteroid (ICS) products varies across the CDR-participating drug plans.

Appendix B: Single entity inhaled corticosteroids and single entity long-acting bronchodilators available in Canada

Drug	Brand Name	Manufacturer	Indication	DIN	Product availability	Cost (\$) for 30 days*
Single entity ICS						
Mometasone	Asmanex Twisthaler	Merck Canada	Asthma	02243595	200 mcg (60DS)	35.00
				02243596	400 mcg(60DS)	70.00
Beclomethasone dipropionate	QVAR	Valeant	Asthma	02242029	50 mcg (200DS)	30.92
				02242030	100 mcg (200DS)	61.65
Budesonide	Pulmicort	Astra Zeneca	Asthma	00852074	100 mcg (200DS)	31.27
				00851752	200 mcg (200DS)	63.86
				00851760	400 mcg (200DS)	93.00
Ciclesonide	Alvesco	Takeda Canada	Asthma	02285606	100 mcg (120DS)	45.54
				02285614	200 mcg (120DS)	75.28
Fluticasone propionate	Flovent HFA	GSK	Asthma	02244291	50 mcg (120DS)	23.93
				02244292	125 mcg (120DS)	41.28
	02244293		250 mcg (120DS)	82.54		
	FloventDiskus		Asthma	02237244	50 mcg (60DS)	15.97**
02237245		100 mcg (60DS)		25.25**		
				02237246	250 mcg (60DS)	41.28
				02237247	500 mcg (60DS)	82.54
Single entity LABA						
Salmeterol	Serevent	GSK	Asthma COPD	02214261	50 mcg (60DS)	56.10
				02231129	50 mcg (60DS)	56.10
Formoterol	Foradil	Novartis	Asthma COPD	02230898	12 mcg (60DS)	50.53
	Oxeze	Astra Zeneca	Asthma Exercise-induced broncho-constriction	02237224 02237225	12mcg (60DS) 6mcg (60DS)	33.65 44.80
Indacaterol	Onbrez Breezhaler	Novartis	COPD	02376938	75 mcg (30DS)	46.50

*Based on costs obtained from the Ontario Drug Benefit Formulary (accessed December 29, 2014)

**Based on costs obtained from McKesson (December 29, 2014)

Appendix C: Public drug plan benefit listings for single entity inhaled corticosteroids and long-acting beta-2 agonists

Public drug plan benefit listings for inhaled corticosteroids

Drug		BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL	YK	NIHB/NU/NT
Mometasone furoate	Asmanex	Ben	No	Ben									
Beclomethasone dipropionate	QVAR	Ben	No	Ben	Ben	Ben							
Budesonide	Pulmicort	Ben											
	Pulmicort nebulas	Res	Ben	Ben	Ben	Pas	Ben	Ben	Res	Res	Res	Ben	Ben
Ciclesonide	Alvesco	Ben											
Fluticasone propionate	Flovent HFA	Ben											
	Flovent Diskus	Ben											

NO=not listed

RES=restricted listing

BEN=unrestricted listing

Public drug plan benefit listings for long-acting beta2-agonists

Drug		BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL	YK	NIHB/NU/NT
Indacaterol	Onbrez	Res	Ben	Res	Ben	Pas	Ben	Res	Res	Res	Res	No	Res
Formoterol	Oxeze Turbuhaler	Res	Ben	Res	Ben	Pas	Ben	Res	Res	Res	Res	Res	Res
	Foradil	Res	Ben	Res	Ben	Pas	Ben	Res	Res	Res	Res	Res	Res
Salmeterol	Serevent Diskus	Res	Ben	Res	Ben	Pas	Ben	Res	Res	Res	Res	Res	Res
	Serevent Diskhaler	Res	Ben	Res	Ben	Pas	Ben	Res	Res	Res	Res	Res	Res

NO=not listed

RES=restricted listing enforced

PAS=restricted listing passive

BEN=unrestricted listing

Ontario Limited Use Criteria

Indacaterol

CODE 443:

For patients with moderate to severe COPD with persistent respiratory symptoms despite an adequate trial of, or an intolerance to, a regularly scheduled short-acting bronchodilator AND a long-acting anticholinergic.

Note: The dose of Onbrez Breezhaler should not exceed 75mcg per day

Salmeterol

CODE 132:

For the treatment of asthma in patients who are using optimum anti-inflammatory treatment and are still experiencing breakthrough symptoms

CODE 391:

For patients with moderate to severe COPD with persistent respiratory symptoms despite an adequate trial of, or an intolerance to, a regularly scheduled short-acting bronchodilator AND a long-acting anticholinergic.

Formoterol

CODE 132:

For the treatment of asthma in patients who are using optimum anti-inflammatory treatment and are still experiencing breakthrough symptoms.

Appendix D: Restriction Criteria for Long-acting Beta Agonists in Canada

Province	Criteria
British Columbia ⁶⁵	<p><i>Salmeterol</i></p> <ol style="list-style-type: none"> 1. Diagnosis of asthma PLUS inadequate response on optimal dose of inhaled corticosteroid OR 2. Diagnosis of COPD PLUS inadequate response on optimal short-acting beta-agonist therapy <p><i>Formoterol</i></p> <ol style="list-style-type: none"> 1. Diganosis of asthma PLUS inadequate response on optimal dose of inhaled corticosteroid <p><i>Indacaterol</i></p> <ol style="list-style-type: none"> 1. Diagnosis of COPD AND inadequate response to optimal short-acting beta-agonist therapy AND dosage does not exceed 75 mcg per day
Saskatchewan ⁶⁶	<p><i>Salmeterol, formoterol</i></p> <p>For treatment of:</p> <ol style="list-style-type: none"> 1. Asthma uncontrolled on concurrent inhaled steroid therapy. It is important that these patients also have access to a short-acting beta-2 agonist for symptomatic relief. 2. COPD unresponsive to short-acting beta agonists or short-acting anticholinergic bronchodilators. <p><i>Indacaterol</i></p> <ol style="list-style-type: none"> 1. For treatment of COPD unresponsive to short-acting beta agonists or short-acting anticholinergic bronchodilators
Ontario	<p><i>Indacaterol</i>: LU CODE 443 For patients with moderate to severe COPD with persistent respiratory symptoms despite an adequate trial of, or an intolerance to, a regularly scheduled short-acting bronchodilator AND a long-acting anticholinergic. Note: The dose of Onbrez Breezhaler should not exceed 75mcg per day</p> <p><i>Salmeterol, formoterol</i>: LU CODE 132 For the treatment of asthma in patients who are using optimum anti-inflammatory treatment and are still experiencing breakthrough symptoms</p> <p><i>Salmeterol</i>: LU CODE 391 For patients with moderate to severe COPD with persistent respiratory symptoms despite an adequate trial of, or an intolerance to, a regularly scheduled short-acting bronchodilator AND a long-acting anticholinergic.</p>

<p>New Brunswick⁶⁷</p>	<p><i>Formoterol, salmeterol, Indacaterol</i></p> <p><u>Chronic Obstructive Pulmonary Disease</u></p> <p>For the treatment of chronic obstructive pulmonary disease (COPD) if:</p> <ul style="list-style-type: none"> • symptoms persist after 2-3 months of short-acting bronchodilator therapy (i.e. salbutamol at a maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day) • For indacaterol only: dose not to exceed 75 mcg/day <p>Coverage can be provided without a trial of short-acting agent if:</p> <ul style="list-style-type: none"> • there is spirometric evidence of at least moderate to severe airflow obstruction (FEV1 < 60% and FEV1 /FVC ratio < 0.7) and significant symptoms i.e. MRC score of 3-5**. <p>Combination therapy with tiotropium AND a long-acting beta2-adrenergic agonist/inhaled corticosteroid (LABA/ICS) will only be considered if:</p> <ul style="list-style-type: none"> • there is spirometric evidence of at least moderate to severe airflow obstruction (FEV1 < 60% and FEV1/FVC ratio < 0.7), and significant symptoms i.e., MRC score of 3-5** AND • there is evidence of one or more moderate-to-severe exacerbations per year, on average, for 2 consecutive years requiring antibiotics and/or systemic (oral or intravenous) corticosteroids. <p>NOTE: If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e. MRC scale). Spirometry reports from any point in time will be accepted.</p> <p>**Medical Research Council (MRC) Dyspnea Scale * Canadian Thoracic Society COPD Classification By Symptom/Disability: Moderate - (MRC 3-4): Shortness of breath from COPD causing the patient to stop after walking about 100 meters (or after a few minutes) on the level. Severe - (MRC 5) Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure. MRC= Medical Research Council Dyspnea Scale</p> <p><i>Formoterol, salmeterol</i></p> <p><u>Reversible obstructive airway disease</u></p> <p>For the treatment of patients, 12 years of age or older, with reversible obstructive airway disease who are using optimal corticosteroid treatment, but are still poorly controlled.</p>
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<p>Nova Scotia⁶⁸</p>	<p><i>Long-acting Beta2-agonists (i.e., Formoterol, Salmeterol, Indacaterol)</i></p> <p><u>Asthma</u></p> <ul style="list-style-type: none"> • for the treatment of moderate to severe asthma in patients who: <ul style="list-style-type: none"> ○ are compliant with inhaled corticosteroids at optimal doses; and ○ require additional symptom control, (e.g., cough, awakening at night, missing activities such as school, work or social activities because of asthma symptoms); and ○ require increasing amounts of short-acting beta2-agonists, indicative of poor control <p><u>Chronic Obstructive Pulmonary Disease</u></p> <ul style="list-style-type: none"> • for the treatment of chronic obstructive pulmonary disease (COPD), if symptoms persist after 2-3 months of short-acting bronchodilator therapy (i.e., salbutamol at a maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day) • coverage can be provided without a trial of short-acting agent if: <ul style="list-style-type: none"> ○ there is spirometric evidence of at least moderate to severe airflow obstruction, (i.e., postbronchodilator values FEV1 < 60% and FEV1/FVC ratio < 0.7), and significant symptoms (i.e., MRC score of 3-5*) • combination therapy with tiotropium and a long-acting beta2 agonist/inhaled corticosteroid will only be considered if: <ul style="list-style-type: none"> ○ there is spirometric evidence of at least moderate to severe airflow obstruction (postbronchodilator values FEV1 < 60% and FEV1/FVC ratio < 0.7), and significant symptoms (i.e., MRC score of 3-5*) <i>and</i> ○ there is evidence of one or more moderate-to-severe exacerbations per year, on average, for 2 consecutive years requiring antibiotics and/or systemic (oral or intravenous) corticosteroids <p><i>NOTE:</i> Coverage of combination therapy with tiotropium and a long-acting beta2 agonist (without an inhaled corticosteroid) will not be considered due to insufficient evidence to support substantial benefit. If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e., MRC scale). Spirometry reports from any point in time will be accepted.</p> <p>* Canadian Thoracic Society COPD Classification By Symptom/Disability: Moderate - (MRC 3-4): Shortness of breath from COPD causing the patient to stop after walking about 100 meters (or after a few minutes) on the level. Severe - (MRC 5) Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure. MRC= Medical Research Council Dyspnea Scale</p>
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<p>PEI⁶⁹</p>	<p><i>Salmeterol, formoterol, indacaterol</i> <u>Asthma</u> For the treatment of asthma when used in patients on concurrent steroid therapy</p> <p><u>Chronic Obstructive Pulmonary Disease</u> For the treatment of mild, moderate, and severe chronic obstructive pulmonary disease (COPD) (i.e. MRC score ≥ 2) in patients who continue to be symptomatic after a 3 month trial of ipratropium at a dose of 12 puffs/day and appropriate use of short-acting beta2-agonists. For the treatment of moderate to severe chronic obstructive pulmonary disease (COPD) (i.e. MRC score 3 to 5) without a trial of short-acting agents (e.g. ipratropium and beta2-agonists) where spirometry shows moderate to severe airflow obstruction (i.e. FEV1 < 60% predicted AND low FEV1/FVC <0.7). A copy of the spirometry report must accompany the Special Authorization.</p> <p>Note: The drug programs will not pay for concurrent use of Tiotropium and Ipratropium. Note: Concurrent use of Tiotropium and long acting beta2-agonists or long acting beta2-agonists/inhaled corticosteroids will only be considered in patients where FEV1 < 60% predicted AND FEV1/FVC <0.7. A copy of the spirometry report must accompany the Special Authorization.</p>
<p>Yukon</p>	<p><i>Salmeterol, formoterol</i> <u>Treatment of asthma</u></p> <ul style="list-style-type: none"> • for patients not adequately controlled on optimal anti-inflammatory treatment <p><u>Treatment of COPD</u></p> <ul style="list-style-type: none"> • For patients with moderate to severe COPD (MRC dyspnea scale score 3 to 5 and spirometric results of FEV1 < 60% and FEV1/FVC < 0.7)
<p>NIHB</p>	<p><i>Salmeterol, formoterol</i> For the treatment of asthma in patients who are using optimal corticosteroid therapy and experiencing breakthrough symptoms requiring regular use of a rapid onset, short duration bronchodilator.</p> <p><i>Salmeterol, indacaterol</i> For the treatment of Chronic Obstructive Pulmonary Disease (COPD) in patients not adequately controlled with ipratropium or tiotropium.</p>

<p>Newfoundland⁷⁰</p>	<p><i>Salmeterol, formoterol</i></p> <p><u>Reversible Obstructive Airway Disease:</u></p> <ul style="list-style-type: none"> • For the treatment of reversible obstructive airway disease where optimal doses of inhaled steroids* are being used and breakthrough symptoms require frequent use of inhaled short-acting bronchodilators. <p>*Optimal defined as: >400mcg/day budesonide >250mcg/day HFA- beclomethasone >250mcg/day fluticasone</p> <p><i>Salmeterol, formoterol, indacaterol</i></p> <p><u>COPD:</u></p> <ul style="list-style-type: none"> • For the treatment of chronic obstructive pulmonary disease (COPD), if symptoms persists after 2-3 months of short-acting bronchodilator therapy (i.e. salbutamol at maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day). • Coverage can be approved without a trial of a short-acting agent if: <ul style="list-style-type: none"> ○ There is spirometric evidence of at least moderate to severe airflow obstruction, i.e. FEV1 < 60% AND FEV1/FVC ratio < 0.7, and significant symptoms i.e. MRC score 3-5.* • For indacaterol: coverage will be limited to a maximum dose of 75 mcg once daily. <p>Coverage of combination therapy with tiotropium and a long-acting beta2 agonist (without an inhaled corticosteroid) will not be considered due to insufficient evidence to support substantial benefit.</p> <p>If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e. MRC scale).</p> <p>* Canadian Thoracic Society COPD Classification By Symptom/Disability: Moderate - (MRC 3-4): Shortness of breath from COPD causing the patient to stop after walking about 100 meters (or after a few minutes) on the level. Severe - (MRC 5) Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure. MRC= Medical Research Council Dyspnea Scale</p>
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Appendix E: Webpages for Provincial Drug Formularies

Province	Webpage for Drug Formulary
British Columbia	http://www.health.gov.bc.ca/pharmacare/benefitslookup/faces/Search.jsp
Alberta	https://idbl.ab.bluecross.ca/
Saskatchewan	http://formulary.drugplan.health.gov.sk.ca/
Manitoba	http://web6.gov.mb.ca/eFormulary/
Ontario	https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp
Quebec	http://www.ramq.gouv.qc.ca/en/regie/legal-publications/Pages/list-medications.aspx
New Brunswick	http://www.gnb.ca/0212/nbpdpformulary-e.asp
Nova Scotia	http://novascotia.ca/dhw/pharmacare/formulary.asp
Prince Edward Island	http://healthpei.ca/formulary
Newfoundland	http://www.health.gov.nl.ca/health/nlmdp/fmlsearch.asp
Yukon Territories	https://apps.gov.yk.ca/pls/apex40p/f?p=161:9000:4324580815029961::::
NIHB (Non-insured Health Benefits) Program	http://www.hc-sc.gc.ca/fniah-spnia/nihb-ssna/provide-fournir/pharma-prod/med-list/index-eng.php

Appendix F: Restriction Criteria for ICS + LABA combination products in Canada

Province	Criteria
British Columbia	<p><i>Advair:</i></p> <ol style="list-style-type: none"> 1. Diagnosis of asthma PLUS inadequate response on optimal dose of inhaled corticosteroid <p>OR</p> <ol style="list-style-type: none"> 2. Diagnosis of COPD PLUS inadequate response on optimal short-acting beta-agonist therapy. <p><i>Symbicort, Zenhale:</i></p> <ol style="list-style-type: none"> 1. Diagnosis of asthma PLUS inadequate response on optimal dose of inhaled corticosteroid
Saskatchewan⁶⁶	<p><i>Advair, Symbicort:</i> For treatment of:</p> <p>(a) Asthma in patients uncontrolled on inhaled steroid therapy. (b) COPD in patients where there has been concurrent or past use of tiotropium or a LABA (salmeterol or formoterol).</p> <p><i>Zenhale:</i> For treatment of asthma in patients uncontrolled on inhaled steroid therapy.</p>
Ontario	<p><i>Advair, Symbicort, Zenhale:</i> For the treatment of asthma in patients who are using optimum anti-inflammatory treatment and are still experiencing breakthrough symptoms</p>
Quebec	<p><i>Advair, Symbicort</i></p> <ol style="list-style-type: none"> 1. for treatment of asthma and other reversible obstructive diseases of the respiratory tract in persons whose control of the disease is insufficient despite the use of an inhaled corticosteroid; 2. for treatment of persons suffering from moderate or severe chronic obstructive pulmonary disease (COPD) whose symptoms are not under control despite the use of an inhaled short-acting β_2 agonist, an inhaled long-acting β_2 agonist and an inhaled anticholinergic agent. 3. For treatment of persons suffering from moderate to severe chronic obstructive pulmonary disease (COPD), who have shown at least one exacerbation of the symptoms of the disease in the last year, despite regular use through inhalation of at least one long-acting bronchodilator; <p>Exacerbation, is understood as a sustained and repeated aggravation of the symptoms requiring intensified pharmacological treatment, for instance, the addition of oral corticosteroids, or a precipitated medical visit or a hospitalization</p> <p><i>Zenhale</i></p> <ol style="list-style-type: none"> 1. for treatment of asthma and other reversible obstructive diseases of the respiratory tract, in persons whose control of the disease is insufficient despite the use of an inhaled corticosteroid;
Yukon	<p><i>Advair, Symbicort</i> Treatment of asthma</p> <ul style="list-style-type: none"> • for patients not adequately controlled on optimal anti-inflammatory treatment • for patients who are stabilized on inhaled corticosteroids & a long-acting beta2-agonist <p>Treatment of COPD</p> <ul style="list-style-type: none"> • For patients with moderate to severe COPD (MRC dyspnea scale score 3 to 5 and spirometric results of FEV1 < 60% and FEV1/FVC < 0.7)

<p>New Brunswick⁶⁷</p>	<p><i>Zenhale:</i> <u>Reversible obstructive airways disease</u> For patients with reversible obstructive airways disease who are</p> <ul style="list-style-type: none"> • Stabilized on an inhaled corticosteroid and a long-acting beta2-adrenergic agonist, <p>OR</p> <ul style="list-style-type: none"> • Using optimal doses of inhaled corticosteroids but are still poorly controlled. <p><i>Advair, Symbicort:</i> <u>Reversible obstructive airways disease</u> For patients with reversible obstructive airways disease who are</p> <ul style="list-style-type: none"> • Stabilized on an inhaled corticosteroid and a long-acting beta2-adrenergic agonist, <p>OR</p> <ul style="list-style-type: none"> • Using optimal doses of inhaled corticosteroids but are still poorly controlled. <p><u>Chronic Obstructive Pulmonary Disease</u> For the treatment of chronic obstructive pulmonary disease (COPD) if:</p> <ul style="list-style-type: none"> • symptoms persist after 2-3 months of short-acting bronchodilator therapy (i.e. salbutamol at a maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day) <p>Coverage can be provided without a trial of short-acting agent if:</p> <ul style="list-style-type: none"> • there is spirometric evidence of at least moderate to severe airflow obstruction (FEV1 < 60% and FEV1 /FVC ratio < 0.7) and significant symptoms i.e. MRC score of 3-5**. <p>Combination therapy with tiotropium AND a long-acting beta2-adrenergic agonist/inhaled corticosteroid (LABA/ICS) will only be considered if:</p> <ul style="list-style-type: none"> • there is spirometric evidence of at least moderate to severe airflow obstruction (FEV1 < 60% and FEV1/FVC ratio < 0.7), and significant symptoms i.e., MRC score of 3-5** AND • there is evidence of one or more moderate-to-severe exacerbations per year, on average, for 2 consecutive years requiring antibiotics and/or systemic (oral or intravenous) corticosteroids. <p>NOTE: If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e. MRC scale). Spirometry reports from any point in time will be accepted.</p> <p>**Medical Research Council (MRC) Dyspnea Scale * Canadian Thoracic Society COPD Classification By Symptom/Disability: Moderate - (MRC 3-4): Shortness of breath from COPD causing the patient to stop after walking about 100 meters (or after a few minutes) on the level. Severe - (MRC 5) Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure. MRC= Medical Research Council Dyspnea Scale</p>
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<p>Nova Scotia⁶⁸</p>	<p><i>Advair, Symbicort, Zenhale:</i></p> <p><u>Asthma</u></p> <ul style="list-style-type: none"> • for the treatment of moderate to severe asthma in patients who: <ul style="list-style-type: none"> ○ are compliant with inhaled corticosteroids at optimal doses; and ○ require additional symptom control, (e.g., cough, awakening at night, missing activities such as school, work or social activities because of asthma symptoms); and ○ require increasing amounts of short-acting beta2-agonists, indicative of poor control <p><u>Chronic Obstructive Pulmonary Disease</u></p> <ul style="list-style-type: none"> • for the treatment of chronic obstructive pulmonary disease (COPD), if symptoms persist after 2-3 months of short-acting bronchodilator therapy (i.e., salbutamol at a maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day) • coverage can be provided without a trial of short-acting agent if: <ul style="list-style-type: none"> ○ there is spirometric evidence of at least moderate to severe airflow obstruction, (i.e., postbronchodilator values FEV1 < 60% and FEV1/FVC ratio < 0.7), and significant symptoms (i.e., MRC score of 3-5*) • combination therapy with tiotropium and a long-acting beta2 agonist/inhaled corticosteroid will only be considered if: <ul style="list-style-type: none"> ○ there is spirometric evidence of at least moderate to severe airflow obstruction (postbronchodilator values FEV1 < 60% and FEV1/FVC ratio < 0.7), and significant symptoms (i.e., MRC score of 3-5*) <i>and</i> ○ there is evidence of one or more moderate-to-severe exacerbations per year, on average, for 2 consecutive years requiring antibiotics and/or systemic (oral or intravenous) corticosteroids <p><i>NOTE:</i> Coverage of combination therapy with tiotropium and a long-acting beta2 agonist (without an inhaled corticosteroid) will not be considered due to insufficient evidence to support substantial benefit.</p> <p>If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e., MRC scale). Spirometry reports from any point in time will be accepted.</p> <p>* Canadian Thoracic Society COPD Classification By Symptom/Disability: Moderate - (MRC 3-4): Shortness of breath from COPD causing the patient to stop after walking about 100 meters (or after a few minutes) on the level. Severe - (MRC 5) Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure. MRC= Medical Research Council Dyspnea Scale</p>
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<p>PEI⁶⁹</p>	<p><i>Advair, Symbicort</i> <u>Asthma</u> For the treatment of asthma in patients who are not well controlled on a regular and adequate course of inhaled steroid therapy prior to the request for combination therapy. Continuation of current coverage requires regular use of an adequate dose of this medication.</p> <p><u>Chronic Obstructive Pulmonary Disease</u> For the treatment of mild, moderate, and severe chronic obstructive pulmonary disease (COPD) (i.e. MRC score \geq 2) in patients who continue to be symptomatic after a 3 month trial of ipratropium at a dose of 12 puffs/day and appropriate use of short-acting beta2-agonists. For the treatment of moderate to severe chronic obstructive pulmonary disease (COPD) (i.e. MRC score 3 to 5) without a trial of short-acting agents (e.g. ipratropium and beta2-agonists) where spirometry shows moderate to severe airflow obstruction (i.e. FEV1 < 60% predicted AND low FEV1/FVC <0.7). A copy of the spirometry report must accompany the Special Authorization.</p> <p>Note: The drug programs will not pay for concurrent use of Tiotropium and Ipratropium. Note: Concurrent use of Tiotropium and long acting beta2-agonists or long acting beta2-agonists/inhaled corticosteroids will only be considered in patients where FEV1 < 60% predicted AND FEV1/FVC <0.7. A copy of the spirometry report must accompany the Special Authorization.</p>
<p>NIHB</p>	<p><i>Advair, Symbicort</i> <u>Reversible obstructive airway disease</u></p> <ul style="list-style-type: none"> For the treatment of reversible obstructive airway disease in patients who are not adequately controlled on medium doses of inhaled corticosteroids (e.g. fluticasone 251-500mcg daily, or the equivalent) as the sole agent and require addition of a long-acting beta agonist. Patients using this combination product must also have access to a short-acting bronchodilator for symptomatic relief. <p><u>Chronic obstructive pulmonary disease</u></p> <ul style="list-style-type: none"> For the treatment of moderate* COPD, if a patient continues to be symptomatic after an adequate trial of a long-acting anticholinergic AND a long-acting beta-agonist OR For the treatment of severe** COPD, if a patient continues to be symptomatic after an adequate trial of a long-acting anticholinergic OR a long-acting beta-agonist <p>*Moderate and **Severe as defined by the Canadian Thoracic Society COPD classification. <u>Moderate</u>: shortness of breath from COPD causing the patient to stop after walking approximately 100 meters (or after a few minutes) on the level. <u>Severe</u>: shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure.</p>

<p>Newfoundland⁷⁰</p>	<p><i>Advair, Symbicort</i></p> <p><u>Reversible Obstructive Airway Disease:</u></p> <ul style="list-style-type: none"> For treatment of asthma in patients in whom a combination of an inhaled steroid and long-acting beta agonist is desirable due to the failure of optimal doses of inhaled steroids *(failure defined as the need for frequent use of inhaled short-acting bronchodilators). <p>*Optimal defined as: >400mcg/day budesonide >250mcg/day HFA- beclomethasone >250mcg/day fluticasone</p> <p><u>COPD:</u></p> <ul style="list-style-type: none"> For the treatment of chronic obstructive pulmonary disease (COPD), if symptoms persists after 2-3 months of short-acting bronchodilator therapy (i.e. salbutamol at maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day). Coverage can be approved without a trial of a short-acting agent if: <ul style="list-style-type: none"> There is spirometric evidence of at least moderate to severe airflow obstruction, i.e. FEV1 < 60% AND FEV1/FVC ratio < 0.7, and significant symptoms i.e. MRC score 3-5.* Combination therapy with tiotropium and a long-acting beta2 agonist/corticosteroid (i.e. Spiriva plus Advair or Symbicort) will only be considered if: <ul style="list-style-type: none"> There is spirometric evidence of a least moderate to severe airflow obstruction (FEV1 < 60% AND FEV1/FVC ratio <0.7), and significant symptoms i.e., MRC score of 3-5. * AND There is evidence of one or more moderate to severe exacerbations per year on average, for 2 years (24 consecutive months) requiring antibiotics and/or systemic (oral or intravenous) corticosteroids. <p>NOTE: Coverage of combination therapy with tiotropium and a long-acting beta2 agonist (without an inhaled corticosteroid) will not be considered due to insufficient evidence to support substantial benefit.</p> <p>If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e. MRC scale).</p> <p>* Canadian Thoracic Society COPD Classification By Symptom/Disability: Moderate - (MRC 3-4): Shortness of breath from COPD causing the patient to stop after walking about 100 meters (or after a few minutes) on the level. Severe - (MRC 5) Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure. MRC= Medical Research Council Dyspnea Scale</p> <p><u>Zenhale</u></p> <p><u>Reversible Obstructive Airway Disease:</u></p> <ul style="list-style-type: none"> For treatment of asthma in patients in whom a combination of an inhaled steroid and long-acting beta agonist is desirable due to the failure of optimal doses of inhaled steroids *(failure defined as the need for frequent use of inhaled short-acting bronchodilators). <p>*Optimal defined as: >400mcg/day budesonide >250mcg/day HFA- beclomethasone >250mcg/day fluticasone</p>
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Appendix G: Interview Questions

How long have you listed ICS+LABAs on your provincial formulary? How are they listed (e.g., restricted, general benefit)?
Why did you decide to list ICS+LABAs this way?
What was the basis for this listing (e.g., quantity limits, general listing)?
Do you have any studies comparing usage/costs before and after implementation of this listing?
Why are certain ICS+LABAs NOT funded?
Do you restrict prescribing to certain specialties (or are certain specialties exempt from restrictions)?

Appendix H: Tiered cost-sharing options

Prescription Drug Plan	Tier 1 (generic)	Tier 2 (preferred brand)	Tier 3 (non-preferred brand)	Tier 4 (specialty)
Plan A	\$5	\$28	\$55	25%
Plan B	\$2	\$20	\$40	N/A
Plan C	\$10	\$25	50%	25%
Plan D	\$4	\$17	75%	25%

Adapted from:

<http://www.cancer.org/treatment/findingandpayingfortreatment/managinginsuranceissues/medicare/medicarepartd/medicare-part-d-formularies-and-drug-coverage>

Appendix I: The British Medical Research Council (MRC) dyspnea scale

Grade (modified MRC)	Description
1 (0)	Not troubled by breathlessness except with strenuous exercise
2 (1)	Troubled by shortness of breath when hurrying on the level or walking up a slight hill
3 (2)	Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level
4 (3)	Stops for breath after walking about 100 yards (90m) or after a few minutes on the level
5 (4)	Too breathless to leave the house or breathless when dressing or undressing

Appendix J: Global Initiative for Chronic Obstructive Lung Disease Severity Classification Tools

A. Classification of Severity of Airflow Limitation in COPD (based on post-bronchodilator FEV1)

Category	Severity	FEV1 predicted*
GOLD 1	Mild	≥80%
GOLD 2	Moderate	50-79%
GOLD 3	Severe	30-49%
GOLD 4	Very severe	<30%

*in patients with FEV1/FVC <0.7

B. Categorization of patients according to risk and severity of disease

Patient Category	Characteristics	Spirometric classification	Exacerbations/ year	CAT	mMRC
A	Low risk, less symptoms	GOLD 1-2	≤1	<10	0-1
B	Low risk, more symptoms	GOLD 1-2	≤1	≥10	≥2
C	High risk, less symptoms	GOLD 3-4	≥2	<10	0-1
D	High risk, more symptoms	GOLD 3-4	≥2	≥10	≥2

CAT: COPD Assessment Test (www.catestonline.org)

mMRC: Modified British Medical Research Council