

FINAL REPORT

Inhaled Corticosteroids (ICS) + Long-Acting Beta-Agonists (LABA) for treatment of asthma

Environmental Scan and Local/Historical Context

March 9th, 2015

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 propionate + salmeterol), Symbicort (budesonide + formoterol), Zenhale (mometasone + formoterol) and BreoEllipta (fluticasone furoate + 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 monthly cost, at the recommended highest dose for asthma, ranges from \$82.90 (Symbicort 6/200 2 inhalations twice daily) to \$138.31 (Advair 50/500 1 inhalation twice daily).

In Ontario, ICS+LABA products (i.e., fluticasone propionate+salmeterol, budesonide+formoterol and mometasone+formoterol) are available on the ODB formulary for the treatment of asthma under the Limited Use program. All public drug programs across Canada fund ICS+LABA products for the management of patients with asthma. Nine of the 12 (75%) public drug programs in Canada list ICS+LABA combination products on a restricted basis (enforced) for the treatment of asthma, requiring special authorization. In two provinces (Alberta and Manitoba), ICS+LABA products are listed as general benefits. Restriction criteria vary slightly across the public drug programs. Inadequate response to optimal dose of inhaled corticosteroid is considered a prerequisite for approval of ICS+LABA products in most jurisdictions.

Part B: Guidelines for the management of patients with asthma

Four guidelines for management of patients with asthma were reviewed: Canadian Thoracic Society (2012 update), Global Initiative for Asthma (2014), British Thoracic Society (2011), and National Heart, Blood and Lung Institute (2007). Guidelines emphasize asthma control, defined as a patient having few or no symptoms, no activity limitations, few or no instances of need for rescue medication, normal lung function and few exacerbations. All guidelines advocate a step-wise approach to the treatment of asthma. All guidelines recommend the use of ICS+LABA, either as a combination inhaler or as two separate inhalers, for the management of patients with asthma, in particular those patients who are uncontrolled on inhaled steroid (e.g., Step 3 in all guidelines).

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

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.

Part D: Rapid Review of Selected Topics

Delivery devices: In a rapid 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 treatment of asthma are available as either DPI (Advair Diskus, Symbicort) or as pressurized MDI (Advair, Zenhale).

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.

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Introduction

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

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

It is estimated that the direct healthcare costs of asthma care in Ontario in 2011 was \$1.6 billion.⁵ The major costs associated with health-care related costs include medications, physician visits and hospitalizations.⁶ Indirect costs mainly due to time loss from work, productivity loss, functional impairment and caregiver time also contribute to the economic burden.⁷ As well, patients with poorly controlled asthma are responsible for the majority of asthma-related resource use.⁸ In a survey conducted in Canada, asthma control and management remained suboptimal with approximately 50% of patients with uncontrolled asthma.⁹ Although there is limited data on the humanistic burden of asthma, studies show a high (31-50%) prevalence of psychological distress and diminished quality of life among asthma patients relative to patients without asthma.⁷

In Canada, there are four ICS+LABA combination products available. Two of these, namely fluticasone propionate+ salmeterol (Advair) and budesonide + formoterol (Symbicort), are indicated for both COPD and asthma. Fluticasone furoate + 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 asthma, 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 asthma (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 propionate+ salmeterol), Symbicort (budesonide + formoterol), Zenhale (mometasone + formoterol) and BreoEllipta (fluticasone furoate+ 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.

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 (Breo Ellipta) for COPD.¹³ 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 COPD.¹⁴ Fluticasone propionate + salmeterol (Advair) and budesonide + formoterol (Symbicort) were available prior to 2003 and thus were not reviewed by the CDR.

Summary

1. Advair and Symbicort were available prior to inception of the Common Drug Review; as such no review was conducted for these products.
2. 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.

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 propionate+ 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)	02408872	2013	59.08**	One inhalation once daily	COPD
			25 + 100 (30DS)			126.60**		

†Based on costs obtained from ODB Formulary (August 26, 2014) *Based on recommended dosages in product monographs¹⁰⁻¹² **Based on costs obtained from McKesson Pharmaclik (August 26, 2014)

Summary

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

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 propionate + 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 A for availability of the single entity ICS and LABA products, Appendix B for listing of LABA products in Canada, and Appendix C for restriction criteria for LABAs in Canada).

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 propionate + salmeterol (Advair), budesonide + formoterol (Symbicort) 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.

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.

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

1. There are currently three ICS+LABA combination products available on the ODB formulary (Limited Use listing) for the treatment of asthma: fluticasone propionate+ salmeterol (Advair, Advair Diskus), budesonide + formoterol (Symbicort) and mometasone + formoterol (Zenhale).

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 D). 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). 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	Ben	No
Ontario	Pas	No	Pas	No	Pas	No
Quebec	Res	Res	Res	Res	Res	No
New Brunswick	Res	Res	Res	Res	Res	No
Nova Scotia	Res	Res	Res	Res	Res	No
PEI	Res	Res	Res	Res	Res	No
Newfoundland	Res	Res	Res	Res	Res	No
Yukon	Res	Res	Res	Res	No	No
NIHB/NT/NU	Res	Res	Res	Res	Res	No

Current as of February 23, 2015.

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 E for detailed criteria for each

jurisdiction with restricted listing status.

Exhibit 3: Summary of Provincial Criteria for fluticasone propionate+ salmeterol (Advair), mometasone + formoterol (Zenhale) and budesonide + formoterol (Symbicort) (for restricted listing for patients with asthma)

Restriction criteria for patients with asthma	BC	SK, PEI	ON	NB	NS	NIHB	YK	QC, NF
Asthma	√	√	√				√	
Asthma (moderate to severe)					√			
Reversible obstructive diseases of respiratory tract				√		√		√
Practitioner exemptions	√							
Inadequate response to optimal dose of inhaled corticosteroid	√	√		√		√		√
Optimum anti-inflammatory treatment and still experiencing breakthrough symptoms			√				√	
Stabilized on inhaled corticosteroids plus a long-acting beta2-agonist				√			√	
Compliant with inhaled corticosteroids at optimal doses					√			
Require additional symptom control					√			
Require increasing amount of short-acting beta2-agonists					√			
Must have access to a short-acting bronchodilator for symptomatic relief.						√		

Summary

1. Nine of the 12 (75%) public drug programs in Canada list ICS+LABA combination products on a restricted basis (enforced) for the treatment of asthma, requiring special authorization. In Ontario, these products are listed as Limited Use products. In two provinces (Alberta and Manitoba), ICS+LABA products are listed as general benefits.
2. Restriction criteria vary slightly across the public drug programs. Inadequate response to optimal dose of inhaled corticosteroid is considered a prerequisite for approval of ICS+LABA products in most jurisdictions.

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 asthma (see Appendix F 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 step therapy for patients with asthma
Alberta	General benefit	No	Individual components listed; less cost of ICS+LABA combination inhaler than 2 separate inhalers
Saskatchewan	Restricted (enforced)	No	No
Manitoba	General benefit	No	Internal review
Ontario	Restricted (passive) FOR ASTHMA ONLY	No	Not applicable
New Brunswick Nova Scotia Newfoundland PEI	Restricted (enforced)	No	The drug class ICS+LABA for COPD and asthma are currently undergoing review by the Atlantic Common Drug Review.
NIHB	Restricted (enforced)	No	No
Yukon	Restricted (enforced)	No	Listed as restricted based on cost

NA: not applicable

Summary

1. The Atlantic Common Drug Review is currently reviewing ICS+LABA combination products for COPD and asthma.
2. Most public drug plans in Canada list ICS+LABA for asthma (and COPD) 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.¹⁵

A tiered co-payment system is a combination of cost-sharing and a preferred drug list.¹⁶ 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.¹⁷ 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 G 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

	Symbicort	Advair	Dulera (Zenhale)	Breo Ellipta
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	Tier 3	Tier 3	Tier 4
Kentucky Preferred Drug List 2014 (www.kentucky.magellanmedicaid.com)	Preferred	Preferred	Preferred	Non-preferred

	Symbicort	Advair	Dulera (Zenhale)	Breo Ellipta
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)	Preferred (Tier 3)

	Symbicort	Advair	Dulera (Zenhale)	Breo Ellipta
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 Symbicort)	Preferred (Step therapy: Step Therapy. Member must first try Asmanex or Qvar.)	Preferred (Member must first try Asmanex or Qvar then maximum therapeutic doses of Dulera, Advair or Symbicort prior to approval. Treatment with single agent ICS therapy and Dulera, Advair or Symbicort must be considered for patients experiencing at least daily asthma symptoms prior to coverage of Breo Ellipta)

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.¹⁸ See Exhibit 6 for ICS+LABA combination products available under PBS for treatment of COPD.

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

Product	Dosage form	Criteria (COPD)
Budesonide+eformoterol (Symbicort Turbuhaler, Symbicort Rapihaler)	100/3 mcg 200/6 mcg 50/3 mcg 400/12 mcg	<p>Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids; OR</p> <p>Patient must have experienced frequent asthma symptoms while receiving treatment with oral or inhaled corticosteroids and require single maintenance and reliever therapy; OR</p> <p>Patient must have experienced frequent asthma symptoms while receiving treatment with a combination of an inhaled corticosteroid and long acting beta-2 agonist.</p> <p>Patient must be aged 12 years or over.</p>
Fluticasone propionate+salmeterol (Seretide) ¹⁹	100/50 mcg 500/50 mcg 250/25 mcg 250/50 mcg 50/25 mcg 125/25 mcg	<p>Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids,</p> <p>AND</p> <p>Patient must have been stabilised on concomitant inhaled salmeterol xinafoate and fluticasone propionate if aged less than 12 years.</p>

Scotland:

See Exhibit 7 for advice for ICS+LABA combination products for asthma in Scotland.²⁰

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

Product	Dosage form	Advice/criteria
Fluticasone propionate + salmeterol (Seretide Evohaler)	50/25 mcg	<p>Seretide 50 Evohaler is accepted for use within NHS Scotland for the regular treatment of asthma where use of a combination of the long-acting beta agonist salmeterol and the inhaled corticosteroid fluticasone is appropriate for a child aged 4-12 years.</p> <p>The acquisition cost of the combination product is less than for the individual components given by aerosol inhalation and for the combination given by Accuhaler (2004)</p>
Budesonide +formoterol (Symbicort SMART)	100/6 mcg 200/6 mcg	<p>budesonide/formoterol turbohaler (Symbicort® SMART®) is accepted for use within NHS Scotland, in adults, for the regular treatment of asthma where use of a combination (inhaled corticosteroid and long-acting beta2-agonist) is appropriate; Symbicort is taken as regular maintenance treatment and as needed in response to symptoms.</p> <p>In patients using inhaled budesonide/formoterol as preventer therapy, use of the same inhaler for reliever therapy is associated with a longer time to first severe exacerbation than use of comparator reliever regimens. In addition, some patients may be able to reduce the dose of preventer therapy (2007)</p>

Summary

1. 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.
2. In Australia, criteria for ICS+LABA combination products for patients with asthma include frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids, or frequent asthma symptoms while receiving treatment with a combination of an inhaled corticosteroid and long acting beta-2 agonist.

Part B: Guidelines for the management of patients with asthma

Various guidelines, both Canadian and international guidelines, have been published for the management of patients with asthma. Guidelines emphasize asthma control, defined as a patient having few or no symptoms, no activity limitations, few or no instances of need for rescue medication, normal lung function and few exacerbations. All guidelines advocate a step-wise approach to the treatment of asthma. A summary of these guidelines is below.

Canadian Guidelines

Canadian Thoracic Society (2012 update)¹

The Canadian guidelines provide recommendations for the diagnosis and management of asthma in children six years of age and older, and adults (Exhibit 8).

Exhibit 8: Canadian Thoracic Society Recommendations for Adults (12 years and older)

Step	Reliever therapy	Recommended regimen	Alternative regimen
First	SABA on demand	Not applicable	Consider starting regular maintenance therapy.
Second	SABA on demand	Inhaled corticosteroid	Leukotriene receptor antagonist
Third	SABA or ICS/LABA used as a reliever (i.e., budesonide/formoterol)	Add LABA	
Fourth	SABA or ICS/LABA used as a reliever	Add LTRA	
Fifth	SABA or ICS/LABA used as a reliever	Prednisone	Anti-IgE

The Canadian Thoracic Society's guidelines for the management of patients with asthma suggest that:

- Regular controller therapy is indicated in individuals who have one or more indicators of poor control.
- Pharmacologic therapy should be determined based upon an individual's current asthma control, escalated if needed to gain control, only after addressing other reasons for poor control, and reduced to the least amount required to maintain asthma control.
- Prescribed controller therapy should take into account both current control and future risk for severe exacerbations.
- SABAs are appropriate relievers for asthma in all age groups and severity, and are the preferred class of reliever for use on demand in all patients with mild asthma
- BUD/FORM as a reliever may be considered in exacerbation-prone individuals 12 years of age and over with moderate asthma and poor control despite fixed-dose maintenance ICS/LABA

combination.

- Use of a single inhaler of BUD/FORM as a reliever and a controller may be of value in select subgroups of individuals 12 years of age and over, particularly exacerbation-prone individuals with uncontrolled asthma despite high maintenance doses of ICS or ICS/LABA combination therapy.
- There is insufficient evidence regarding the initiation of a fixed-dose ICS+LABA combination with a SABA as a reliever as part of a self-management plan for children and adults on no controller therapy or on ICS monotherapy experiencing an acute loss of asthma control.

International Guidelines

Global Initiative for Asthma (GINA) (2014)²¹

Evidence-based guidelines for asthma diagnosis and management were recently updated by Global Initiative for Asthma (GINA). Pharmacologic treatment strategies for patients with COPD are found in Exhibit 9.

Exhibit 9: Global Initiative for Asthma (GINA): Stepwise approach to control symptoms and minimize future risk

Step (reliever)	Preferred controller	Other options
1 (SABA)		Consider low-dose ICS
2 (SABA)	Low-dose ICS	Leukotriene receptor antagonists, low-dose theophylline
3 (SABA or low-dose ICS+formoterol)	Low-dose ICS+LABA	Med/high dose ICS, low-dose ICS+LTRA (or + theophylline)
4 (SABA or low-dose ICS+formoterol)	Med+high ICS+LABA	High dose ICS+LTRA (or + theophylline)
5 (SABA or low-dose ICS+formoterol)	Refer for add-on treatment (e.g., anti-IgE)	Add low-dose oral corticosteroids

Medications and strategies for symptoms control: key points

- At present, Step 1 treatment is with as-needed SABA alone. However, chronic airway inflammation is found even in patients with infrequent or recent-onset asthma symptoms, and there is a striking lack of studies of inhaled corticosteroids (ICS) in such populations.
- Treatment with regular daily low dose ICS is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization and death.
- For patients with persistent symptoms and/or exacerbations despite low-dose ICS, consider step-up but first check for common problems such as inhaler technique, adherence, persistent

allergen exposure and comorbidities.

- For adults and adolescents, the preferred step-up treatment is combination ICS/LABA.
- For adults and adolescents with exacerbations despite other therapies, the risk of exacerbations is reduced with combination low-dose ICS/formoterol (with beclometasone or budesonide) as both maintenance and reliever, compared with maintenance controller treatment plus as-needed SABA>
- Consider step-down once good asthma control has been achieved and maintained for about 3 months, to find the patients' lowest treatment that controls both symptoms and exacerbations
 - Provide the patient with a written asthma action plan, monitor closely and schedule a follow-up visit.
 - Do not completely withdraw ICS unless this is needed temporarily to confirm the diagnosis of asthma.

British Thoracic Society (2011)²²

The British guidelines provide recommendations for best practice in the management of asthma in children, adolescents and adults.

Statement on Combination Inhalers

In efficacy studies, where there is generally good compliance, there is no difference in efficacy in giving inhaled steroid and a long-acting beta-2 agonist in combination or in separate inhalers. In clinical practice, however it is generally considered that combination inhalers aid compliance and also have the advantage of guaranteeing that the long-acting beta2-agonist is not taken without the inhaled steroids.

Exhibit 10: British Thoracic Society for Management of Asthma

Step	Adults	Children aged 5-12 years
1 (mild intermittent asthma)	Inhaled SABA as required	Inhaled SABA as required
2 (regular preventer therapy)	Add inhaled steroid 200-800 mcg/day	Add inhaled steroid 200-400 mcg/day (or other preventer drug)
3 (initial add-on therapy)	Add inhaled LABA (if no response, increase dose of steroid)	Add inhaled LABA (if no response, increase dose of steroid)

Step	Adults	Children aged 5-12 years
4 (persistent poor control)	Increase inhaled steroid up to 2000 mcg/day OR Addition of fourth drug (e.g., leukotriene receptor antagonist, theophylline, oral beta2-agonist)	Increase inhaled steroid up to 800 mcg/day
5 (continuous or frequent use of oral steroids)	Use daily steroid tablet (Consider other treatments to minimize the use of steroid tablets) Maintain high-dose inhaled steroid at 2000 mcg/day	Use daily steroid tablet Maintain high-dose inhaled steroid at 800 mcg/day

SABA: short-acting beta2-agonist

LABA: long-acting beta2-agonist

National Heart, Lung and Blood Institute (2007)²³

Recommendations for the diagnosis and management of asthma were developed by the National Asthma Education and Prevention Program (see Exhibit 11).

Exhibit 11: Stepwise Approach for Managing Asthma in Youths ≥12 years of age and Adults

Step	Preferred	Alternative
1	SABA prn	NA
2	Low-dose ICS	Cromolyn, LTRA, nedocromil or theophylline
3	ICS+LABA or medium-dose ICS	Low-dose ICS + either LTRA or theophylline
4	Medium dose ICS + LABA	Medium-dose ICS + either LTRA or theophylline
5	High-dose ICS + LABA	Consider omalizumab for patients with allergies
6	High-dose ICS + LABA + oral corticosteroid	Consider omalizumab for patients with allergies

Guidelines for use of ICS/LABA combination products

All guidelines use a step therapy approach to treatment; if patient has uncontrolled symptoms or exacerbations, a step up to the next level is indicated. Similarly, if symptoms are controlled for 3 months and there is a low risk for exacerbations, a step down to the previous level is recommended.²¹

The combination of ICS + LABA (either as a single inhaler or as two separate inhalers) is recommended as a controller in all guidelines for management of patients with asthma. In particular, ICS+LABA is indicated in patients who are uncontrolled on inhaled steroid i.e., patients should be tried on ICS alone prior to the addition of a LABA (i.e., Step 3). The Canadian guidelines state that for patients 12 years of

age and older who remain uncontrolled on low-dose ICS, the addition of a LABA is recommended, ideally in the form of a combination inhaler. A combination inhaler is preferred over the use of two single inhalers in order to prevent patient error, as LABAs should never be used alone (as monotherapy) for asthma.²⁴ In addition, the use of budesonide-formoterol (Symbicort) as a reliever may be considered in exacerbation-prone individuals 12 years of age and over with moderate asthma and poor control despite fixed-dose maintenance ICS/LABA combination.¹

Summary

Guidelines emphasize asthma control, defined as a patient having few or no symptoms, no activity limitations, few or no instances of need for rescue medication, normal lung function and few exacerbations. All guidelines advocate a step-wise approach to the treatment of asthma.

All guidelines recommend the use of ICS+LABA, either as a combination inhaler or as two separate inhalers, for the management of patients with asthma, in particular those patients who are uncontrolled on inhaled steroid (i.e., Step 3 in all guidelines).

Budesonide+formoterol can be used as a reliever in exacerbation-prone individuals with moderate asthma and poor control despite fixed-dose maintenance ICS/LABA combination.

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 asthma AND health services accessibility OR treatment outcome OR drug utilization review OR managed care programs OR insurance pharmaceutical services. All articles were restricted to adult population only. Bibliographies of identified articles were scanned for additional relevant articles.

Results

Cost-sharing programs for patients with asthma

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.²⁵ At least three different types of cost sharing have been used in various plans including deductibles, co-insurance and co-payments.²⁵ In a review, a total of 132 articles were identified showed an association between prescription drug cost sharing and outcomes (including pharmacy utilization and spending, medical care utilization and spending, and health outcomes).²⁶ Overall, regardless of drug

class, increased cost sharing is associated with lower rates of drug treatment, worse adherence among existing users and more frequent discontinuation of therapy. Cost sharing increases of 10% (through either higher co-payments or coinsurance) were associated with a 2-6% decline in prescription drug use or expenditures.

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.²⁷ 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.²⁸ 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.

Using data from database of the Regie de l'assurance maladie du Quebec (RAMQ), comparison of monthly consumption of three classes of medications (inhaled corticosteroids, neuroleptics, anticonvulsants) was reviewed before and after implementation of a cost-sharing drug insurance plan.²⁹ For individuals receiving social assistance and using inhaled corticosteroids (regardless of indication), a statistically significant decrease of 37% of the monthly consumption was noted for 11 months following implementation of the new cost sharing plan.

In Iceland in 2010, reimbursement of fixed ICS+LABA combinations related to any diagnosis was shifted to the patient. A population-based, retrospective, observational study investigated the impact of the policy change on medication and healthcare utilization in patients with asthma and/or COPD that was previously controlled.³⁰ Overall, there were 48% fewer fixed ICS+LABA combinations dispensed after implementation of the policy change. This was associated with 44% more healthcare visits, more oral

corticosteroid use (76%) and SABA (51%) use.

Data from the United States have shown similar results. The impact of increasing patient prescription copayments for long-term asthma controller medications on asthma-related medication use and healthcare services was evaluated.³¹ Among patients receiving ICS+LABA combination therapy as well as patients on leukotriene receptor antagonists, a copayment of \$5 or greater was associated with more asthma-related outpatient visits and emergency department visits compared with the <\$5 group.

Other reimbursement options

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 propionate + salmeterol) by measuring the rate of asthma-related emergency department visits and hospitalizations.³² This study was conducted in Quebec where a prior authorization process was introduced in 2003 to limit the non-optimal 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 pre-process 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.

The use of ICS+LABA combination therapy is recommended in patients 12 years and older whose disease is uncontrolled by standard therapy. There have been several studies that have evaluated whether patients started on ICS+LABA therapy had previous claims for controller medications or a history of asthma-related health care use (e.g., emergency room visits, hospitalization).³³⁻³⁵ Three retrospective studies of data from US commercial health insurance databases found that only between 31% and 40% of patients met criteria for use of prior controller medications or had a history of asthma-related health care use.

One study evaluated adherence and persistence to ICS (alone or in combination with LABA) in patients with private or public drug coverage in Quebec.³⁶ Overall, both cohorts had low levels of adherence and persistence to ICS therapy, although patients privately insured were significantly less adherent than patients publicly insured (mean difference: -9.7%; 95% CI: -13.2% to -6.5%). As well, patients privately insured were found to be 52% more likely to stop ICS during the first year than patients publicly insured (adjusted HR=1.5; 95% CI: 1.2 to 2.0).

Summary

1. 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.
2. 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.

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.³⁷ However, specific inhalation techniques are needed for proper use of each of the devices; incorrect technique can result in potentially reduced efficacy. Poor inhaler technique, as well as patient compliance, is an important determinant of asthma control.³⁸ In an observational study that assessed the prevalence of inhaler technique in patients with COPD and asthma, older age ($p=0.008$), lower schooling ($p=0.001$) and lack of instruction on inhaler technique ($p<0.001$) were associated with inhaler misuse. As well, inhaler misuse was associated with increased risk of hospitalization ($p=0.001$), emergency room visits ($p<0.001$), courses of oral steroids ($p<0.001$) and antimicrobials ($p<0.001$).³⁹

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, and are only indicated in Canada for the management of patients with asthma.

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 This same report found that 74% and patients using a DPI and 43% using a pressurized MDI + spacer made at least one error during administration. There are potential reasons for inhaler errors including the device (e.g., physical skill, manipulation, dexterity requirements), patient preference for inhalers (e.g., operational use, convenience) and lack of education from healthcare providers on proper use of the device.⁴³

In another systematic review and meta-analysis, for adult patients with asthma in the outpatient setting, there were no differences in pulmonary function response or symptom scores noted when inhaled corticosteroid is used via a DPI or MDI with spacer/holding chamber.³⁷ The authors suggest that selection of an appropriate aerosol delivery device should be based on patient's ability to use the device

correctly, the preferences of the patient for the device, the availability of the drug/device combination, the compatibility between drug and delivery device, the lack of time or skills to educate patients, cost of therapy and potential for reimbursement.

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.⁴⁴ However, in patients able to use an MDI correctly, spacers do not improve the clinical effect of the medication administered.⁴⁴ 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, and toilet tissue cores. 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.⁴⁵

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.⁴⁶ The difference in the results may have been due to inclusion of patients with poor MDI technique.⁴⁵ 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.^{47;48}

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.⁴⁵

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.⁴⁹ 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.^{44 45} 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.⁵⁰ However, it should be noted that many of ICS+LABA combination products approved for use in Canada (with the exception of Advair and Zenhale) are only available in dry powder inhaler format. See Appendix H for public plan funding of spacers in Canada.

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;51;52} In contrast to MDIs, multi-dose DPIs incorporate dose counters.⁴¹

Single-use DPIs (e.g., Spiriva HandiHaler) must be loaded before each inhalation, and this may require opening blister packs that contain the medication capsules; no ICS+LABA approved for management of asthma in Canada is available as a single-use DPI.⁵³ Advair Diskus and Symbicort Turbuhaler are multi-dose DPIs and contain more than one dose of the drug. Regardless of whether the device is single- or multi-dose DPI, 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

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.³⁷ 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.⁵³

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.⁵⁴ 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/advaire-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).⁵⁵ 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.⁵⁶ 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.⁵⁷⁻⁵⁹ 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.⁶⁰ 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.⁶¹

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.

Single maintenance and reliever therapy for asthma

ICS+LABA is used for the treatment of patients with moderate to severe asthma. It is often prescribed as a standard fixed-dose maintenance regimen along with a short-acting beta-agonist for relief of symptoms.⁶² However, budesonide-formoterol has also been used for both maintenance and as-needed reliever use (SMART: single combination budesonide-formoterol inhaler maintenance and reliever therapy).⁶³ The SMART regimen has been used, especially in patients 12 years of age and older, who are

prone to exacerbations and continue to have uncontrolled asthma despite treatment with ICS or ICS+LABA.^{1;64;65} The Canadian guidelines and GINA 2014 guidelines include the use of a single inhaler of BFC as a reliever and a controller as an option for select patient groups.^{1;21} Neither mometasone+formoterol (Zenhale) nor fluticasone propionate+salmeterol (Advair) is not approved for maintenance and reliever therapy, but only as maintenance therapy. Formoterol, even though classified as a long-acting bronchodilator, is also considered a fast-acting beta-agonist. In patients with asthma, formoterol has a bronchodilatory action that is as rapid as that of salbutamol; the median reported time to onset of significant bronchodilation is between 3 and 12 minutes for formoterol.⁶⁶ Health Canada has approved budesonide+formoterol (Symbicort) in a single inhaler for use in patients 12 years of age and older as both a controller and a reliever. The use of a single inhaler ICS+LABA as a reliever and a controller may be beneficial for some patients as some self-management approaches to loss of asthma control permit the patient to adjust the combination product on a day-to-day basis.¹ This results in greater inhaled corticosteroid and LABA use when symptoms are worse.

A Cochrane review of 13 trials (N=13152 adults) compared the use of a single inhaler of budesonide-formoterol as a reliever and a controller compared with maintenance with inhaler corticosteroids and any reliever.⁶⁵ The odds of experiencing exacerbations requiring treatment with oral steroids were lower with single-inhaler therapy compared with control (OR 0.83;95% CI 0.70-0.98, eight trials). However, for patients whose asthma was not well-controlled on ICS, reduction in hospital admission with single inhaler of budesonide-formoterol did not reach statistical significance (OR 0.81;95% 0.45, 1.44).

In another Cochrane review, the efficacy and safety of budesonide-formoterol in a single inhaler as a reliever and a controller was compared with controller treatment through combination ICS+LABA inhalers along with additional fast-acting beta-agonists for relief of symptoms.⁶⁷ Four studies (N=9130) were included: two were 6-month double-blind studies and two were 12-month open-label studies. Compared with higher fixed-dose combination inhalers, fewer people using budesonide-formoterol in a single inhaler had exacerbations requiring hospitalization or a visit to the ER (OR 0.72, 95% CI 0.57-0.90) and fewer had exacerbations requiring a course of oral corticosteroids (OR 0.75, 95% CI 0.65, 0.87).

Summary

Systematic reviews and meta-analysis suggest that single-therapy inhaler with budesonide-formoterol in patients with moderate or severe asthma may result in a reduction in the rate of exacerbations, compared to current best practice and combination inhalers (steroid+LABA plus SABA). It should be noted that all of the published trials of single inhaler therapy with budesonide-formoterol have been funded by Astra-Zeneca.^{65;68} The Canadian Thoracic guidelines state: *We suggest the use of a single inhaler of budesonide/formoterol as a reliever and a controller at the same ICS dose be considered in individuals 12 years of age and over with asthma uncontrolled on fixed-dose ICS+LABA combination therapy in lieu of increasing the ICS dose of the combination therapy.*¹

ICS+LABA via two separate inhalers or combination inhaler

A literature review was done to assess whether fixed-dose combinations achieve greater asthma control compared with the monocomponents administered as separate inhalers. Fixed combination inhalers are more convenient for patients and may increase adherence since only one inhaler needs to be taken.⁶⁹ A retrospective longitudinal study determined that the use of ICS and LABA monocomponents is associated with a higher risk of exacerbations and higher reliever use than fixed ICS+LABA combinations via a single inhaler.⁷⁰ A meta-analysis showed that fluticasone propionate+salmeterol fixed combination had a greater effect on morning peak expiratory flow compared to two separate inhalers (difference=5.4 L/min; p=0.006). However, this small difference did not translate into symptomatic benefits in terms of number of symptom-free and reliever-free days and nights.⁷¹

Due to the potential safety concerns of LABAs used alone in patients with asthma, some guidelines recommend the use of ICS+LABA combination therapy in order to avoid the potential use of LABA monotherapy.²¹

Summary

There have been limited studies that have directly assessed adherence to ICS+LABA as combination therapy compared to ICS plus LABA administered via separate inhalers.

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>)

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 propionate+ salmeterol), Symbicort (budesonide + formoterol), Zenhale (mometasone + formoterol) and BreoEllipta (fluticasone furoate + 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 monthly cost, at the recommended highest dose for asthma, ranges from \$82.90 (Symbicort 6/200 2 inhalations twice daily) to \$138.31 (Advair 50/500 1 inhalation twice daily).

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.
 - The LU code 330 states: For the treatment of asthma in patients who are using optimum anti-inflammatory treatment and are still experiencing breakthrough symptoms

Public Plan Listing in Canada

- Nine of the 12 (75%) public drug programs in Canada list ICS+LABA combination products on a restricted basis (enforced) for the treatment of asthma, requiring special authorization. In two provinces (Alberta and Manitoba), ICS+LABA products are listed as general benefits.
- Restriction criteria for ICS+LABA combination products for management of asthma include:
 - History of asthma
 - Inadequate response to optimal dose of inhaled corticosteroid
 - Breakthrough asthma symptoms despite optimum anti-inflammatory treatment
 - Stabilized on inhaled corticosteroids plus a long-acting beta2 agonist

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

- Four guidelines were reviewed: Canadian Thoracic Society (2012 update), Global Initiative for Asthma (2014), British Thoracic Society (2011), and National Heart, Blood and Lung Institute (2007).
- Guidelines emphasize asthma control, defined as a patient having few or no symptoms, no activity limitations, few or no instances of need for rescue medication, normal lung function and few exacerbations. All guidelines advocate a step-wise approach to the treatment of asthma.
- All guidelines recommend the use of ICS+LABA, either as a combination inhaler or as two separate inhalers, for the management of patients with asthma, in particular those patients who are uncontrolled on inhaled steroid (e.g., Step 3 in all guidelines).

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

- 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 suggested that this translated to more healthcare visits and more oral corticosteroid and SABA use.
- 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.

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 treatment of asthma are available as either DPI (Advair Diskus, Symbicort) or as pressurized MDI (Advair, Zenhale).

- 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.
- Single maintenance and reliever therapy for asthma
 - Systematic reviews and meta-analysis suggest that single-therapy inhaler with budesonide-formoterol in patients with moderate or severe asthma may result in a reduction in the rate of exacerbations.

Health Equity

Across Canada, ICS+LABA combination products are available in every jurisdiction for the treatment of patients with asthma. In Ontario, 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, formoterol).

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 asthma recommend the use of ICS+LABA for the management of patients with asthma, in particular those patients who are uncontrolled on inhaled steroid

In Canada, all public drug programs fund ICS+LABA combination products for the treatment of asthma. In Ontario, ICS+LABA products are available on the ODB formulary 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: 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 02243596	200 mcg (60DS) 400 mcg(60DS)	35.00 70.00
Beclomethasone dipropionate	QVAR	Valeant	Asthma	02242029 02242030	50 mcg (200DS) 100 mcg (200DS)	30.92 61.65
Budesonide	Pulmicort	Astra Zeneca	Asthma	00852074 00851752 00851760	100 mcg (200DS) 200 mcg (200DS) 400 mcg (200DS)	31.27 63.86 93.00
Ciclesonide	Alvesco	Takeda Canada	Asthma	02285606 02285614	100 mcg (120DS) 200 mcg (120DS)	45.54 75.28
Fluticasone propionate	Flovent HFA	GSK	Asthma	02244291 02244292 02244293	50 mcg (120DS) 125 mcg (120DS) 250 mcg (120DS)	23.93 41.28 82.54
	FloventDiskus		Asthma	02237244 02237245 02237246 02237247	50 mcg (60DS) 100 mcg (60DS) 250 mcg (60DS) 500 mcg (60DS)	15.97** 25.25** 41.28 82.54
Single entity LABA						
Salmeterol	Serevent	GSK	Asthma COPD	02214261 02231129	50 mcg (60DS) 50 mcg (60DS)	56.10 56.10
Formoterol	Foradil	Novartis	Asthma COPD	02230898	12 mcg (60DS)	50.53

Drug	Brand Name	Manufacturer	Indication	DIN	Product availability	Cost (\$) for 30 days*
	Oxeze	Astra Zeneca	Asthma Exercise-induced bronco- 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 B: 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

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 C: Restriction Criteria for Long-acting Beta Agonists in Canada

Province	Criteria
British Columbia ⁷²	<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. Diagnosis 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 ⁷³	<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

Province	Criteria
Ontario	<p>Indacaterol: 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>Salmeterol, formoterol: 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>Salmeterol: 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>

Province	Criteria
New Brunswick ⁷⁴	<p><i>Formoterol, salmeterol, Indacaterol</i></p> <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) • 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> 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>

Province	Criteria
Nova Scotia ⁷⁵	<p data-bbox="428 233 1252 264"><i>Long-acting Beta2-agonists (i.e., Formoterol, Salmeterol, Indacaterol)</i></p> <p data-bbox="428 306 521 338"><u>Asthma</u></p> <ul data-bbox="428 342 1422 583" style="list-style-type: none"> • for the treatment of moderate to severe asthma in patients who: <ul data-bbox="526 380 1422 583" 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 data-bbox="428 625 899 657"><u>Chronic Obstructive Pulmonary Disease</u></p> <ul data-bbox="428 661 1442 1230" 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 data-bbox="526 842 1414 947" 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 data-bbox="526 1020 1442 1230" 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 data-bbox="428 1272 1430 1371"><i>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.</i></p> <p data-bbox="428 1377 1393 1476"><i>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.</i></p> <p data-bbox="428 1518 1414 1766"> <i>* 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</i> </p>

Province	Criteria
PEI ⁷⁶	<p><i>Salmeterol, formoterol, indacaterol</i></p> <p><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>
Yukon	<p><i>Salmeterol, formoterol</i></p> <p><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)
NIHB	<p><i>Salmeterol, formoterol</i></p> <p>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></p> <p>For the treatment of Chronic Obstructive Pulmonary Disease (COPD) in patients not adequately controlled with ipratropium or tiotropium.</p>

Province	Criteria
Newfoundland ⁷⁷	<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>

Appendix D: 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-fourrir/pharma-prod/med-list/index-eng.php

Appendix E: 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
Saskatchewan⁷³	<p><i>Advair, Symbicort:</i> For treatment of: (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>

Province	Criteria
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 β2 agonist, an inhaled long-acting β2 agonist and an inhaled anticholinergic agent. 3. <input type="checkbox"/> 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></p> <p>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)

Province	Criteria
New Brunswick ⁷⁴	<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>

Province	Criteria
Nova Scotia ⁷⁵	<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>

Province	Criteria
PEI ⁷⁶	<p><i>Advair, Symbicort</i></p> <p><u>Asthma</u></p> <p>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></p> <p>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.</p> <p>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.</p> <p>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>

Province	Criteria
NIHB	<p><i>Advair, Symbicort</i></p> <p><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>

Province	Criteria
Newfoundland ⁷⁷	<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 ipatropium 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>

Appendix F: 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 G: 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 H: Public plan funding of spacers (holding chambers) in Canada

British Columbia	Not funded	NA	NA
Alberta	Yes	Aerochamber Optichamber Space Chamber Vortex	Funded under Health Care Insurance Plan 1 spacer device every 12 months
Saskatchewan	Yes	Aerochamber	Funded under Supplementary Health Program, Medical Supplies and Appliances
Manitoba	Yes	Aerochamber	Funded under Manitoba Health Pharmacare
Ontario	Not funded	NA	NA
Quebec	Yes	Aerochamber	Information obtained from www.trudellmed.com
PEI	Not funded	NA	NA
Nova Scotia	Yes	Aerochamber	Funded under Nova Scotia Formulary
New Brunswick	Not funded	NA	NA
Newfoundland	Yes	Aerochamber	Funded under Prescription Drug Program 1 spacer device every 12 months
NIHB	Yes	Aerochamber Optichamber EZ Spacer Pocket Chamber	Funded under NIHB 1 spacer device every 12 months
Yukon			