

FINAL REPORT

Long-acting muscarinic antagonists (LAMA) for treatment of chronic obstructive pulmonary disease (COPD)

Environmental Scan and Local/Historical Context report

December 12, 2014

Executive Summary

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

In Canada, there are three long-acting muscarinic antagonists (LAMA, also known as long-acting anticholinergics) products available: tiotropium (Spiriva), glycopyrronium bromide (Seebri Breezhaler) and aclidinium (Tudorza). These products are indicated solely for the management of patients with COPD. Another single LAMA product, umeclidinium (Incruse Ellipta), has been approved by Health Canada for the management of patients with COPD but is not yet marketed. There are two LAMA+long-acting beta-agonists (LABA) combination products for the management of patients with COPD that were introduced onto the Canadian market in 2014: indacaterol + glycopyrronium (Ultibro) and vilanterol + umeclidinium (Anoro Ellipta). No generic formulation is available for any of these products. The cost of a one-month supply for the single entity products ranges from \$53 (glycopyrronium) to \$68 (aclidinium); the cost of the combination products is approximately \$85/month.

In Ontario, tiotropium, aclidinium and glycopyrronium are available on the ODB formulary as a general benefit listing. Nine of the 12 (75%) public drug programs in Canada list LAMA products on a restricted basis for the treatment of COPD, requiring special authorization. In three provinces (Alberta, Ontario and Quebec), Spiriva and Seebri Breezhaler are listed as general benefits. Various reimbursement schemes are used as funding models for LAMAs in international jurisdictions including prior authorization or use of a preferred product.

Part B: Guidelines for the management of patients with COPD

Five guidelines were reviewed: Canadian Thoracic Society (2008), Global Initiative for Chronic Obstructive Lung Disease (2014), Institute for Clinical Systems Improvement (2013), NICE Guidance for COPD (2011) and American College of Physicians, American College of Chest Physicians, American Thoracic Society and the European Respiratory Society Guideline (2011). All guidelines recommend the use of a LAMA or a LABA product for patients with mild to moderate COPD. Use of a LAMA and a LABA in combination is only recommended in 2 guidelines: Canadian Thoracic Guideline and the GOLD guidelines (2014). Triple therapy (LAMA, ICS + LABA) is recommended in all guidelines for patients with severe COPD.

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

Despite these agents being restricted through the use of prior authorization in both Canada and international jurisdictions, there is a paucity of literature assessing these reimbursement schemes for adherence or outcome measures (e.g., exacerbation rates, hospitalization). One study from British Columbia suggests that the implementation of a prior authorization process for tiotropium was associated with an increase in emergency admissions for COPD, despite an increase in use of tiotropium.

Part D: Rapid Review of Selected Topics

Delivery Devices: All LAMA and LABA+LAMA products are available in Canada as dry powder inhalers (DPIs). However, there are several types of DPIs on the market including single-unit devices (e.g.,

Handihaler, Breezhaler) and multi-dose units (e.g., Genuair, Ellipta). There are 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.

LAMAs in treatment of asthma: There is accumulating evidence that tiotropium added to standard therapy in patients with uncontrolled moderate to severe asthma may improve lung function, as measured by PEF and FEV1. However, to date, quality of life improvements have not been measured in any of the studies. In only one study, tiotropium reduced the risk of a severe exacerbation when compared to placebo. Further clinical trials are needed prior to recommending the addition of a LAMA for patients with inadequately controlled moderate to severe asthma.

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Introduction

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

The worldwide prevalence of COPD is more than 10% among adults aged 40 years and older.⁴ In Ontario, there are 850,000 (11.8% of the population) diagnosed with COPD.⁵ In a study using Ontario data, the prevalence of COPD increased by 64.8% between 1996 and 2007 (76% in women and 55% in men, $p < 0.001$).⁶ However, approximately 60-85% of patients, mainly with mild to moderate disease, are thought to remain undiagnosed, as many patients may only seek treatment when symptoms are severe.⁷ Canadian data indicate similar findings for underdiagnosis of COPD. Among Canadians aged 35 to 79 years, 4% reported having been diagnosed by a health professional with COPD, chronic bronchitis or emphysema.⁸ However, spirometry data collected by the Canadian Health Measures Survey (CHMS) revealed that 13% of Canadians aged 35 to 79 had an FEV1/FVC ratio less than 0.70 (measured airflow obstruction consistent with COPD). This is more than 3 times greater than the self-reported diagnosis of COPD of 4%.

The burden of COPD in Canada is significant. The Canadian Institute for Health Information (CIHI) showed that COPD accounted for the highest rate of hospital admission among major chronic illnesses in Canada.⁹ In addition, approximately one in five patients with COPD (18.8%) were readmitted to acute inpatient care within 30 days of discharge.¹⁰ Using data from Ontario, people with COPD had rates of hospitalizations, emergency room visits and ambulatory care visits that were 63%, 85% and 48% higher than the rest of the population.⁵ COPD exacerbations are the major drivers for COPD morbidity and mortality, as well as most important component for direct healthcare costs.¹¹ Using a dynamic simulation model, the annual societal cost of COPD in Canada (cost, morbidity and mortality) was estimated at \$4.52 billion Canadian dollars in 2011.¹² Patients with COPD also have a high symptom burden.¹³ Patients with advanced COPD have symptoms that are comparable to those patients with cancer or congestive heart failure.¹⁴

Management strategies for patients with COPD include smoking cessation, drug therapy and educational programs. Treatment goals are to prevent disease progression, relieve symptoms, improve exercise tolerance and prevent exacerbations. Drug therapy includes use of a bronchodilator to control symptoms with use of inhaled corticosteroid (ICS) in patients with more severe disease.¹ Bronchodilators are the cornerstone of treatment for patients with COPD and include beta2-agonists (short-acting and long-acting: SABA and LABA) and muscarinic antagonists (also known as anticholinergics; short-acting and long-acting: SAMA and LAMA). Inhaled corticosteroids are generally used in combination with a long-acting bronchodilator for management of patients with moderate to

severe COPD.

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

The objectives of this report are:

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

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

Availability and Costs of LAMA products in Canada

In Canada, there are three single LAMA products available: tiotropium (Spiriva), glycopyrronium bromide (Seebri Breezhaler) and aclidinium (Tudorza). These products are indicated solely for the management of patients with COPD. Another single LAMA, umeclidinium (Incruse Ellipta) has been approved by Health Canada for the management of patients with COPD but is not yet marketed. There are two LAMA+LABA combination products for the management of patients with COPD that were introduced onto the Canadian market in 2014: indacaterol + glycopyrronium (Ultibro) and vilanterol + umeclidinium (Anoro Ellipta). All products are available as dry powder inhalers. There are currently no generic products available. Exhibit 1 outlines the dosage forms and costs for LAMA products (including LAMA + LABA combination products).

Exhibit 1: LAMA products (including LAMA+LABA combination products) available in Canada

Drug Name	Brand name	Device	mcg/spray (package size)	DIN #	Monthly Cost (30 days)*	Dosing	Approved indications
LAMA single entity products							
Acclidinium	Tudorza Genuair	DPI	400 mcg (60 DS)	02409720	53.10 ^{††}	Twice daily	COPD
Glycopyrronium bromide	Seebri Breezhaler	DPI	50 mcg (30 DS)	02394936	53.10 ^{††}	Once daily	COPD
Umeclidinium	Incruse Ellipta	DPI	62.5 mcg	02423596	NA	Once daily	COPD
Tiotropium	Spiriva	DPI	18 mcg (30 DS)	02246793	65.01 ^{††}	Once daily	COPD
LAMA+LABA combination products							
Umeclidinium + vilanterol	Anoro Ellipta	DPI	62.5/25mcg	02418401	85.46 [†]	Once daily	COPD
Glycopyrronium + indacaterol	Ultibro Breezhaler	DPI	50/100mcg	02418282	84.83 [†]	Once daily	COPD

*Based on recommended dosages in product monographs¹⁵⁻¹⁷

†Based on costs obtained from McKesson

††Based on costs obtained from the Ontario Drug Benefit Formulary (Accessed: December 12, 2014)

Summary

- Three LAMA single entity products are available on the Canadian market, for the indication of COPD.
- The medications are packaged as a one-month supply (using the recommended doses for COPD).
- The monthly cost ranges from \$53.10 for Seebri Breezhaler and Tudorza Genuair to \$65.01 for tiotropium (Spiriva).
- Two LAMA+LABA combination products have been approved for sale in Canada: Anoro Ellipta and Ultibro.

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. Glycopyrronium (Seebri) and acclidinium (Tudorza) have been reviewed by the CDR. Ultibro was reviewed by CDR in December 2014; it was recommended that this product be listed with criteria (see Appendix A for summary of CDEC recommendation) . Anoro Ellipta is currently being reviewed by the CDR.

Exhibit 2: Common Drug Review for LAMA products

Generic name	Trade Name	Common Drug Review
Glycopyrronium bromide	Seebri Breezhaler (May 2013)	<p>Be listed for treatment of chronic obstructive pulmonary disease with the following condition: List in a manner similar to tiotropium</p> <p><u>Reasons for Recommendation:</u></p> <ol style="list-style-type: none"> Two randomized controlled trials (RCTs) (GLOW-1 and GLOW-2) demonstrated statistically significant improvements in trough FEV1 with glycopyrronium compared with placebo. GLOW-1, GLOW-2 and a network meta-analysis suggested that glycopyrronium and tiotropium have similar efficacy for improving lung function in patients with COPD. At recommended doses, the daily cost of glycopyrronium (\$1.77 for 50 mcg) is less than the daily cost of tiotropium (\$2.17 for 18 mcg).
Acclidinium bromide	Tudorza Genuair (Apr 2014)	<p>Be listed for the treatment of chronic obstructive pulmonary disease (COPD) if the following conditions are met:</p> <ul style="list-style-type: none"> List in a manner similar to other long-acting antimuscarinic antagonists (LAMAs). Drug plan costs for acclidinium bromide should not exceed the cost of any other LAMA. <p><u>Reasons for the Recommendation:</u></p> <ol style="list-style-type: none"> Six double-blind randomized controlled trials (RCTs) demonstrated statistically significant improvements in trough FEV1 with acclidinium bromide compared with placebo and suggested similar efficacy as compared with tiotropium and formoterol in patients with moderate to severe COPD. At the recommended dose, the daily cost of acclidinium bromide is less than the daily cost of tiotropium (\$2.17), but more than the cost of glycopyrronium bromide (\$1.77).

Summary

- No review of tiotropium (Spiriva) was conducted by the CDR, as it was available prior to the inception of the CDR.
- The manufacturers of Anoro Ellipta and Ultibro have requested a review of their products; they are currently being reviewed by the CDR.
- Seebri was reviewed by the Common Drug Review in May 2013 for the indication of COPD; a recommendation was made to list this product similar to tiotropium (Spiriva). Tudorza was reviewed in April 2014, with a recommendation to be listed in a manner similar to other LAMA products.

LAMA product listing in Ontario

General Benefit (GB)

In Ontario, tiotropium, aclidinium and glycopyrronium bromide are available as general benefit on the ODB formulary with a therapeutic note [i.e., Anticholinergic agents should be used with extreme caution in the elderly due to age-related central nervous system adverse effects (e.g., confusion, paranoia, hallucinations). Avoid in patients with dementia as drug-induced memory impairment is common. (This does not apply to ipratropium bromide)]. The LAMA+LABA combination products have not been reviewed by the CDR, and are not listed 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. Long-acting beta2-agonists (LABAs) (see Appendix B for availability of the single LABA products, Appendix C for listing of LABA products in Canada, and Appendix D for restriction criteria for LABAs in Canada) are available as Limited Use products in Ontario. It is likely that some patients are being treated with dual LAMA and LABA therapy using the available products.

Committee to Evaluate Drugs:

The Committee to Evaluate Drugs (CED) is the Ministry of Health and Long-term care's independent expert advisory committee on drug-related issues. The CED reviewed and recommended listing for glycopyrronium (Seebri Breezhaler) and tiotropium (Spiriva).

Spiriva was reviewed in 2003 by the CED (formerly known as the Drug Quality and Therapeutics Committee: DQTC). It was recommended that Spiriva be listed as a General Benefit based on the available evidence. As well, it was suggested that a retrospective database study to evaluate the difference between COPD-related hospitalization rates for patients on tiotropium and ipratropium be conducted.

The manufacturer of Seebri submitted a request for review to CED for the indication of COPD in May 2013. The recommendation was that Seebri Breezhaler be recommended for listing on the ODB Formulary as a General Benefit in September 2013.

Summary

- There are currently three LAMA single entity products available on the Ontario Drug Benefit formulary as general benefit listing: tiotropium (Spiriva), aclidinium (Tudorza) and glycopyrronium (Seebri).

Public Plan Listings in Canada

Part 1: Listing Status

In order to determine the listing of LAMA products across Canada, the relevant webpages of the provincial drug formularies were searched (See Appendix E). In Canada, all public plans provide coverage for at least one LAMA product for eligible patients. These products are available either as a general benefit or as a restricted benefit. The restricted benefit is enforced (e.g., prescriber is required to provide information, often in writing, regarding justification for use of LAMA products). Tiotropium, which was the first LAMA product available in 2002, is listed on all formularies. Glycopyrronium and aclidinium were available on the Canadian market in 2013. Anoro Ellipta and Ultibro received their NOC in December 2013 and were marketed in 2014.

A summary of the various listings (see Exhibit 3) is as follows:

Tiotropium

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

Glycopyrronium

- General benefits without restrictions: Alberta, Ontario, Quebec
- Restricted (enforced): British Columbia, Saskatchewan, Manitoba, Nova Scotia, New Brunswick, Yukon, NIHB/NU/NT
- Not listed: Prince Edward Island, Newfoundland

Aclidinium

- General benefits without restrictions: Quebec, Ontario
- Not listed: British Columbia, Alberta, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland, NIHB/NU/NT, Yukon

Exhibit 3: Public plan listings in Canada for LAMA products

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

No=not listed;

Res=restricted listing - enforced

Ben=unrestricted listing

Restriction Criteria

In order for patients to be eligible for publically funded LAMAs, 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 4. See Appendix F for detailed criteria for each jurisdiction with restricted listing status.

Exhibit 4: Summary of Provincial Criteria for LAMA products

Restriction criteria for COPD patients	BC	SK	NB, NS, PEI, NL	NIHB, NT, NU	YK	MB
Inadequate response after 3 months ipratropium	√			√		√
Practitioner exemptions	√					
Diagnosis of COPD: FEV1 ≤65% and FEV1/FVC<0.7	√					
Unresponsive to short-acting beta-agonists or short-acting anticholinergics		√	√		√	
Treatment of moderate to severe COPD (MRC dyspnea scale 3-5) with spirometry if no trial of short-acting agents		√	√	√		
Moderate to severe COPD treatment with spirometry results					√	
Combination of LAMA plus ICS+LABA considered if moderate/severe airflow obstruction, symptoms and exacerbations			√			
Combination of LAMA and LABA will not be considered due to insufficient evidence			√*			
Combination of LAMA and SAMA not covered			√**			

*for Nova Scotia, Newfoundland; **for PEI

Summary

- Nine of the 12 (75%) public drug programs in Canada list LAMA products on a restricted basis for the treatment of COPD, requiring special authorization. In three provinces (Alberta, Ontario and Quebec), Spiriva and Seebri Breezhaler are listed as general benefits.
- Restriction criteria vary among the public drug plans including spirometry results for confirmation of COPD (2 plans), prior use of SABA and/or SAMA (7 plans) OR if no trial of short-acting agents, then spirometry results (4 plans).

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 LAMAs (see Appendix G for interview questions). Exhibit 5 summarizes the information obtained in the interviews.

Exhibit 5: 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)	No (listed in 2007)	Listed as restricted based on cost of tiotropium compared to ipratropium, and not substantial evidence of much difference in efficacy
Alberta	General benefit	No	Not applicable
Saskatchewan	Restricted (enforced)	2008: after publication of Canadian guidelines, criteria reviewed for Exception Drug Status Program	Internal review after publication of Canadian COPD guidelines
Manitoba	Restricted (enforced)	No	Placed on restricted listing as concerned about use in asthma and wanted to ensure that ipratropium and LAMAs not used together
Ontario	General benefit	No	Not applicable

New Brunswick Nova Scotia Newfoundland PEI	Restricted (enforced)	Reviewed in 2008 with the following changes for criteria for special authorization: <ul style="list-style-type: none"> Patients with spirometric evidence of moderate to severe airflow obstruction will be eligible for coverage of one long-acting bronchodilator (e.g. tiotropium, salmeterol, or formoterol) without a trial of maximum doses of a short-acting bronchodilator. Patients with spirometric evidence of moderate to severe airflow obstruction and with more frequent exacerbations* will be eligible for coverage of both tiotropium and a long-acting beta2 agonist (LABA)/inhaled corticosteroid combination. 	Atlantic Common Drug Review (2008) based on publication of Canadian COPD guidelines The drug class ICS+LABA for COPD and asthma are currently undergoing review by the Atlantic Common Drug Review.
NIHB	Restricted (enforced)	Spiriva reviewed and added to formulary in 2003 <ul style="list-style-type: none"> Not substantial evidence of much difference in efficacy between tiotropium and ipratropium Seebri added to formulary in 2013	Not applicable
Yukon	Restricted (enforced)	None	Listed as restricted based on cost and possible misdiagnosis of COPD

NA: not applicable

Summary

- Most public drug plans in Canada list LAMAs 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 in the United States. 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 Illinois (Medicaid), the preferred inhaled anticholinergic (long-acting) is Spiriva; Tudorza Pressair is the non-preferred inhaled anticholinergics.¹⁸

A tiered co-payment system is a combination of cost-sharing and a preferred drug list.¹⁹ 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.²⁰ In a five-tier system, tier 1 includes preferred generic drugs, tier 2 non-preferred generic drugs, tier 3 preferred brand drugs, tier 4 non-preferred brand drugs and tier 5 specialty drugs (e.g., injectables) (see Appendix H for examples of copayments with tiered formulary systems). See Exhibit 6 for some sample listings of LAMA products in the United States. Note: Seebri and Ultibro Breezhalers are not commercially available in the United States.

Exhibit 6: Listing of LAMA products (single entity or combination) in the United States*

Spiriva	Spiriva	Tudorza	Anoro Ellipta
AETNA Preferred List (Chronic Medications: Asthma) (3-Tier system) (www.aetna.com)	Tier 2	Tier 3 (precertification: a diagnosis of COPD and a documented contraindication or intolerance or allergy or failure of an adequate trial of one week of preferred bronchodilator, Spiriva)	Not listed
Amerigroup Medication Formulary (Medicaid markets in Florida, Louisiana, Maryland, Nevada, New Jersey and Washington) (www.providers.amerigroup.com)	Preferred brand-name therapy	Not listed	Not listed
Blue Cross Blue Shield of South Carolina Preferred Drug List (www.southcarolinablues.com)	Preferred	Not listed	Not listed
Blue Cross Blue Shield of Texas Standard Preferred Drug List (January 2014) (www.bcbstx.com)	Preferred	Not listed	Not listed
Connecticut Medicaid Preferred Drug List (www.ctdssmap.com)	Preferred	Not listed	Not listed
Idaho Medicaid Preferred Drug List (www.healthandwelfare.idaho.gov)	Preferred	Non-preferred	Not listed
Illinois Medicaid Preferred Drug List http://www2.illinois.gov/hfs/sitecollectiondocuments/pdl.pdf	Preferred	Non-preferred (i.e., prior authorization required)	Non-preferred (i.e., prior authorization required)
Kaiser Permanente 2014 Medicare Part D Comprehensive Formulary (5-tier system) (www.healthy.kaiserpermanente.org)	Tier 3	Tier 4	Not listed
Kentucky Preferred Drug List 2014 (www.kentucky.magellanmedicaid.com)	Preferred	Non-preferred	Not listed
Oregon Fee-for-Service Enforceable Physical Health Preferred Drug List 2014 (http://www.oregon.gov/oha/healthplan/pages/tools_prov/pdl.aspx)	Preferred	Not listed	Not listed
Texas Medicaid Preferred Drug List (http://www.txvendordrug.com/pdl/)	Preferred	Non-preferred (prior authorization required)	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)	Tier 4	Preferred (Tier 3)	Not listed

Wellmark Prior authorization/Step therapy (http://www.wellmark.com/HealthAndWellness/DrugInformation/PharmacyHome.aspx)	Tier 2	Tier 4	Not listed
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*Note: Seebri Breezhaler and Ultibro Breezhaler are not available in the United States.

Other Countries

Australia:

In Australia, the Pharmaceutical Benefits Scheme (PBS) restricts LAMA products to patients with COPD.²¹ See Exhibit 7 for LAMA products available under PBS for treatment of COPD.

Exhibit 7: LAMA products for COPD (Australia)

Product	Dosage form	Listing
Tiotropium (Spiriva)	18 mcg capsules for inhalation	Restricted benefit: chronic obstructive pulmonary disease (COPD)
Glycopyrronium (Seebri Breezhaler)	50 mcg inhalation	

New Zealand:

Special authority is required for reimbursement for tiotropium (Spiriva).²² Special authority criteria define the clinical circumstances of patients who can receive funding for the medicine. Special Authority applications are processed by Ministry of Health Services; the majority of Special Authority applications are processed electronically, often while the patient is still with the prescriber.

The criteria for approval for Spiriva are as follows:

1. To be used for the long-term maintenance treatment of bronchospasm and dyspnoea associated with COPD; and
2. In addition to standard treatment, the patient has trialed a short acting bronchodilator of at least 40 mcg ipratropium q.i.d for one month; and
3. Either:

The patient's breathlessness according to the Medical Research Council (UK) dyspnoea scale is:

- Grade 4 (stops for breath after walking about 100 meters or after a few minutes on the level); or
- Grade 5 (too breathless to leave the house, or breathless when dressing or undressing); and

Applicant must state recent measurement of:

4. All of the following:
 - Actual FEV1 (litres); and
 - Predicted FEV1 (litres); and
 - Actual FEV1 as a % of predicted (must be below 60%); and
5. Either:
 - Patient is not a smoker (for reporting purposes only); or
 - Patient is a smoker and has been offered smoking cessation counselling; and
6. The patient has been offered annual influenza immunisation.

Scotland:

In Scotland, Spiriva Handihaler and Seebri Breezhaler are considered step one therapy for inhaled anticholinergics.²³ Spiriva Respimat is restricted to patients who have poor manual dexterity and may have difficulty using the Handihaler device. See Exhibit 8 for advice for LAMA products in Scotland.

Exhibit 8: LAMA products for COPD (Scotland)

Product	Dosage form	Advice/criteria
Tiotropium Respimat inhaler (Spiriva Respimat)	2.5 mcg	Tiotropium respimat inhaler (Spiriva Respimat®) is accepted for restricted use within NHS Scotland as maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease. It may be used for patients in whom tiotropium is an appropriate choice of maintenance bronchodilator treatment but it is restricted to patients who have poor manual dexterity and therefore have difficulty using the Handihaler device.(2007) ²⁴
Glycopyrronium (Seebri Breezhaler)	44mcg for inhalation	This product is accepted for use within NHS Scotland.
Vilanterol + umeclidium (Anoro)	NA	For review (targeted date July 2014)

Summary

- In the United States, most health plans list Spiriva as preferred LAMA on their formularies with Tudorza as non-preferred. Anoro Ellipta is currently being reviewed by many drug plans, and as such, is not yet listed.
- In Australia, both Spiriva and Seebri Breezhaler are funded, as a restricted benefit for COPD. New Zealand fund Spiriva using the Special Authority process.

Part B: Guidelines for the management of patients with COPD

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

Canadian Guidelines

Canadian Thoracic Society (2008)²⁵

The Canadian Thoracic Society's classification of severity is based on symptoms and disability (see Exhibit 9). The number of annual exacerbations is also used in classifying patients according to their COPD severity.

Exhibit 9: Canadian Thoracic Society COPD classification

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

MRC: Medical Research Council (see Appendix I)

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

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

corticosteroid) with theophylline as indicated.

International Guidelines

Global Initiative for Chronic Obstructive Lung Disease (2014)²⁶

Evidence-based guidelines for COPD diagnosis, management and prevention were recently updated by Global Initiative for Chronic Obstructive Lung Disease (GOLD). Although previous versions of GOLD treatment recommendations were based solely on spirometry (i.e., lung function), the most recent edition uses other factors such as number of exacerbations and patient's symptoms, to classify patients (see Appendix J). Treatment strategies for patients with COPD are found in Exhibit 10.

Exhibit 10: Global Initiative for Chronic Obstructive Lung Disease (GOLD): Treatment of Patients with COPD (Global Initiative for Chronic Obstructive Lung Disease)²⁶

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

SABA: short-acting beta2-agonist

SAMA: short-acting muscarinic antagonist

LABA: long-acting beta2-agonist

LAMA: long-acting muscarinic antagonist

ICS: inhaled corticosteroid

PDE4: phosphodiesterase-4

Institute for Clinical Systems Improvement (2013)²⁷

An evidence-based guideline for people with symptoms of stable COPD, as well as acute exacerbations of COPD in the outpatient setting was published in 2013 by ICSI. Recommendations for treatment strategies (see Exhibit 11) are based on COPD severity as predicted by lung function (using definitions as proposed by GOLD).

Exhibit 11 Institute for Clinical Systems Improvement Guidelines for Management of COPD²⁸

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

NICE Guidance for COPD (2011)²⁹

The pharmacotherapy guidelines for COPD are as follows:

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

American College of Physicians, American College of Chest Physicians, American Thoracic Society and the European Respiratory Society have endorsed the following recommendations (2011)³⁰

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

American College of Chest Physicians and Canadian Thoracic Society Guideline: Prevention of acute exacerbations of chronic obstructive pulmonary disease (2014)³¹

A review of literature and practice-based guidelines was done to provide recommendations (total of 33) for prevention of acute exacerbations in patients with COPD. For long-acting bronchodilators, specifically LAMAs, the following recommendations were made:

- Recommendation 13: In patients with moderate to severe COPD, we recommend the use of a LAMA compared to placebo to prevent moderate to severe acute exacerbations of COPD.
- Recommendation 14: In patients with moderate to severe COPD, we recommend the use of LAMA compared to LABA to prevent moderate to severe acute exacerbations of COPD.
- Recommendation 23: For patients with stable COPD, we recommend LAMA+LABA or LAMA monotherapy, since both are effective to prevent acute exacerbations of COPD.
- Recommendation 24: For patients with stable COPD, we recommend maintenance combination of ICS+LABA or LAMA monotherapy, since both are effective to prevent acute exacerbations of COPD.
- Recommendation 25: For patients with stable COPD, we suggest maintenance ICS+LABA plus LAMA or LAMA monotherapy, since both are effective to prevent acute exacerbations of COPD.

Guidelines for use of LAMA products

Monotherapy

LAMA products (with LABA products as alternatives) are recommended in all guidelines. However, there is some variability as to when LAMA monotherapy is initially recommended, based on severity of disease. Guidelines grade severity of disease based on FEV1 measurements, symptoms and/or number of exacerbations per year. A comparison of the various guidelines and what stage of disease LAMA

products are initially recommended, is shown in Exhibit 12.

Dual therapy

The combination of a LAMA and a LABA is recommended in two treatment guidelines for COPD. The Canadian Thoracic Society guidelines recommend the combination of a LAMA and LABA in patients with moderate disability and lung function impairment.²⁵ According to the GOLD criteria, LAMA+LABA dual therapy is recommended as a treatment alternative for group B (high symptoms/low risk), C (low symptoms/high risk), and D (high symptom/ high risk) patients.²⁶

Triple therapy

Triple therapy (i.e., LAMA, LABA and ICS) is recommended in most guidelines for patients with severe disease. For example, in the Canadian Thoracic Society guidelines, triple therapy is recommended in patients with frequent acute exacerbations of COPD (one or more per year).²⁵

Exhibit 12: Comparison of guidelines for initial treatment with LAMA (or LAMA+LABA)

Guideline	Stage of disease LAMA first recommended	Combination therapy (LAMA + LABA)
American College of Physicians, American College of Chest Physicians, American Thoracic Society and the European Respiratory Society	Symptomatic patients and FEV1 <60% predicted	Not stated
NICE Guidance for COPD	FEV1 ≥50% predicted	Not stated
Global Initiative for Chronic Obstructive Lung Disease (GOLD)	First choice: Group B (low risk, more symptoms) Alternative therapy: Group A (low risk, less symptoms)	Alternative therapy: Group B (low risk, more symptoms)
Institute for Clinical Systems Improvement	Moderate (FEV1 50-79% predicted)	Not stated
Canadian Thoracic Society	Mild	Long-acting bronchodilators (i.e., LABAs and long-acting anticholinergics) are added on to short-acting bronchodilators in patients with persistent disability.

Summary

- All guidelines recommend the use of a LAMA or a LABA product for patients with mild to moderate COPD.
- Use of a LAMA and a LABA in combination (not stated if 2 inhalers or as 1 inhaler) is only recommended in 2 guidelines: Canadian Thoracic Guideline and the GOLD guidelines (2014).
- Triple therapy (LAMA, ICS + LABA) is recommended in all guidelines for patients with severe COPD.

Part C: Impact of different drug reimbursement schemes for LAMA products for COPD

Methods

A literature search was conducted in Pubmed using the terms: (tiotropium or aclidinium or glycopyrronium or scopolamine derivatives or muscarinic antagonists or cholinergic antagonists) AND chronic obstructive pulmonary disease AND (health services accessibility OR treatment outcome OR drug utilization review OR managed care programs OR insurance pharmaceutical services OR reimbursement mechanisms). Bibliographies of identified articles were scanned for additional relevant articles.

Results

Cost-sharing programs for patients with COPD

Cost sharing programs are used in many countries for several reasons including the promotion of appropriate utilization of health care services and the reduction for the demand for health care services.³² At least three different types of cost sharing have been used in various plans including deductibles, co-insurance and co-payments.³²

The impact of fixed co-payment and income-based cost-sharing policies was assessed on the use of inhaled medications (for both asthma and COPD) in British Columbia.³³ 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.³⁴ 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.

Prior Authorization

The impact of British Columbia's coverage of tiotropium was assessed in a time series analysis using data from BC's centralized administrative healthcare databases. Starting in July 2007, BC provided reimbursement for tiotropium via a prior authorization process based on criteria for pulmonary function and previous responsiveness to treatment with ipratropium bromide. Patients of respirologists could receive coverage without having to satisfy the prior authorization criteria. Over the 2.5 year period after public coverage, tiotropium use increased by 24% (95% CI 23.9-24.8) more than predicted. Ipratropium use decreased 9.9% (95% CI -9.4 to -10.3) more than predicted during the same period. Visits to physicians were unchanged, but there were between 596-948 more emergency admissions for COPD and between 582-1940 more hospital admissions of any kind than were predicted from pre-policy data. By covering tiotropium for some patients, the total amount of out-of-pocket spending decreased by approximately 19.4% (CDN\$2.97 million). Therefore, the benefits of public drug plan coverage for tiotropium in BC were reduction in out-of-pocket costs for patients and private insurers. However, no reduction in hospitalizations or physician visits were observed.³⁵

Summary

- Based on the limited data available for cost-sharing options for inhaled medications used for COPD and asthma, increasing the amount that a patient is required to pay for a medication, either through higher deductibles or via co-insurance, may result in patients being less likely to initiate or continue treatment with an inhaled medication.
- One study from British Columbia suggests that the implementation of a prior authorization process for tiotropium was associated with an increase in emergency admissions for COPD, despite an increase in use of tiotropium.

Part D: Rapid Review of Selected Topics

Methods of Drug Delivery: Dry Powder Inhalers

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.³⁶ However, specific inhalation techniques are needed for proper use of each of the devices; incorrect technique can result in potentially reduced efficacy. Two common modes of inhalational delivery include the pressurized metered-dose inhaler and the breath-actuated dry powder inhalers (DPI). In Canada, the LAMA products, including LABA+LAMA, are only available as DPIs. Therefore, the focus of this rapid review will be DPIs only.

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.³⁷⁻³⁹ In contrast to MDIs, most multi-dose DPIs incorporate dose counters.⁴⁰

DPIs must be loaded before each inhalation, and this may require opening blister packs that contain the medication capsules (for single-unit devices).⁴¹ There is a potential to use the DPI device incorrectly, including failure to exhale before actuation and failure to hold the breath after inhaling.³⁷ In one study, the error rate associated with DPI technique increased with age and with the severity of airway obstruction.⁴² For example, with the Turbuhaler, the error rate was 25.4% in subjects less than 60 years of age and 46% in those over the age of 60 ($p<0.05$, OR 0.4; 95% CI 0.18-0.90). As well, error rates were 25% with normal lung function and 64% with severe obstruction including those patients with COPD ($p<0.05$). 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 ($p<0.001$).⁴³

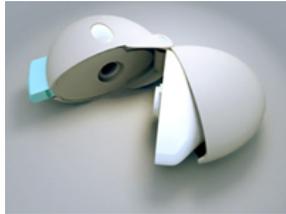
Patients with COPD who are experiencing an exacerbation, low inspiratory flow rates may limit the use of DPIs.⁴⁴ However, most patients who can perform adequate spirometry can usually generate a sufficient peak inspiratory flow rate to operate most DPIs.⁴⁵ For example, Turbuhaler DPI, which showed the greatest dependence on flow rate in simulation studies, has been successfully used in patients with COPD worsening.⁴⁵

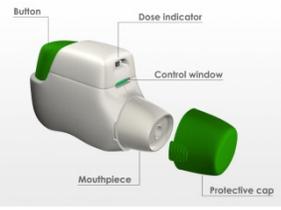
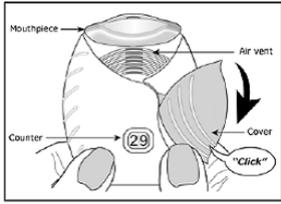
In single-unit dose devices (e.g., Handihaler, Breezhaler), the drug is supplied in individual single-dose gelatin capsules which must be inserted into the unit before use. After use, the remains of the gelatin

capsule must be removed before the next capsule can be placed in the device.⁴⁶ Single-dose DPIs can be confusing and difficult for patients to use due to the extra “loading” step required.⁴⁷ Multi-dose DPIs contain more than one dose of the drug. There are two types of multi-dose DPIs: reservoir and multi-unit dose devices. Multi-dose reservoir devices contain a bulk supply of drug from which individual doses are released with each actuation, whereas multi-unit dose DPIs utilize individual prepared and sealed doses of drug.

Factors to consider when choosing a device include the patients’ ability to use the inhaler device properly (e.g., cognitive function and dexterity and strength), device use with multiple medications (i.e., choosing the same type of device may reduce the potential for confusion), the cost and reimbursement of a device with the desired medication, device convenience and patient preference for a device.⁴⁸ Patient preference for a specific inhaler is important, as patient’s experiences may have an influence on adherence and possible long-term outcomes.^{49;50} In one study that examined relationships between patient satisfaction and treatment compliance, an association was observed between increasing treatment compliance and fewer exacerbations ($p < 0.001$) and fewer hospitalizations due to exacerbations ($p < 0.001$).⁵⁰ In one study, the multi-dose DPIs (Genuair and Diskus) were both easier to use and preferred by patients than single dose DPIs (e.g., Handihaler). The inhaler characteristics that appeared to have the most influence on patients’ preference were the presence of multiple dosage and ease of drug dose preparation.^{51;52}

Exhibit 13: Comparison of Dry Powder Inhalers available with LAMA and LABA+LAMA products

Device Name	Drugs Available	Comments
Single-unit dose		
Handihaler 	Tiotropium (Spiriva)	Requires insertion of capsule from a blister pack into device, use of 2 inhalations, and removal of gelatin capsule after use; requires dexterity to load High internal resistance and patients may have problems achieving an adequate inhalation rate
Breezhaler 	Glycopyrronium (Seebri) Glycopyrronium + indacaterol (Ultibro)	Low-airflow resistance device suitable for patients with a range of COPD severities ⁵³ Requires insertion of capsule from a blister pack into device, and removal of gelatin capsule after use; requires dexterity to load
Multi-dose reservoir		

<p>Genuair</p> 	<p>Aclidinium (Tudorza)</p>	<p>Lock out safety feature once all doses have been delivered (to prevent use of device without drug) No need to insert capsule into device before inhalation Disposable device Dose counter to provide user with number of remaining treatments Feedback mechanisms (e.g., audible click, coloured control window) to confirm successful dose inhalation</p>
Multi-unit dose		
<p>Ellipta</p> 	<p>Umeclidinium + vilanterol (Anoro)</p> <p>Umeclidinium (Incruse)</p>	<p>Dose counter to provide user with number of remaining treatments No need to insert capsule into device before inhalation; doses prepared for inhalation when cover opened</p>

Summary

All LAMA and LABA+LAMA products are available in Canada as DPIS. However, there are several types of DPIS on the market including single-unit devices (e.g., Handihaler, Breezhaler) and multi-dose units (e.g., Genuair, Ellipta). 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.⁴¹

Long-acting anticholinergics in patients with asthma

The use of LAMAs has recently been explored in patients with inadequately controlled persistent asthma. Previous studies using the short acting anticholinergic ipratropium in patients with persistent asthma reported no benefit with routine use.⁵⁴ As well, the Canadian guidelines for diagnosis and management of asthma do not recommend the use of ipratropium in the management of patients with asthma.⁵⁵ However, anticholinergics with a longer half-life (e.g., tiotropium) may help control persistent asthma symptoms and exacerbations. In addition, these agents may allow for a reduction in corticosteroid requirements.⁵⁶ A summary of the RCTs evaluating tiotropium in asthma is found below. It should be noted that tiotropium is not officially indicated for the treatment of asthma in Canada.

Tiotropium was evaluated in 210 patients with inadequately controlled persistent asthma in a double-blind, triple-dummy crossover trial.⁵⁷ The objectives were to assess whether the addition of tiotropium was superior to a doubling of the dose of an inhaled glucocorticoid and noninferior to a LABA +ICS. Treatment groups received 14 week course of beclomethasone 80 mcg twice daily plus tiotropium 18 mcg daily, beclomethasone 80 mcg twice daily plus salmeterol 50 mcg twice daily or beclomethasone 160 mcg twice daily with matching placebos. There was a 2-week washout between each phase when patients only received beclomethasone 80 mcg twice daily. The primary outcome was morning peak expiratory flow rate (PEF). Tiotropium was superior to double-dose ICS, with a morning PEF 25.8 L/min

higher than those who received double-dose beclomethasone (95% CI 14.4-37.1; $p < 0.001$). The addition of tiotropium was noninferior to the addition of salmeterol for all outcomes assessed. Several limitations were identified with this study including use of a low dose of beclomethasone during washout periods, and use of PEF (considered a surrogate measure for asthma control) as primary outcome.⁵⁶ A follow-up study attempted to describe predictors of a positive clinical response.⁵⁸ Overall, an acute response to a short-acting bronchodilator (especially salbutamol), predicted a positive clinical response to tiotropium for FEV1 (OR 4.08; 95% CI 2.00-8.31; $p < 0.001$). As well, patients with a higher cholinergic tone (predicted via inference from a lower resting heart rate) was also a predictor for a positive clinical response to tiotropium.

The efficacy and safety of tiotropium compared to salmeterol and placebo was evaluated in 388 patients with moderate to severe asthma who were uncontrolled with ICS alone.⁵⁹ Enrollment was limited to asthma patients homozygous for arginine at the 16th amino acid position of the beta2-adrenergic receptor (B16-Arg/Arg). After a 4-week run and 4-week follow-up period, patients were randomly assigned to tiotropium 5 mcg Respimat, salmeterol 50 mcg bid, or placebo for 16 weeks. The primary endpoint was change in morning PEF. Tiotropium was more effective than placebo and not inferior to salmeterol (PEF: difference -0.78 L/min; 95% CI -13.096 to 11.53; $p = 0.002$). Asthma exacerbations occurred in patients from each treatment group (tiotropium 12.5/5, salmeterol 12.7%, placebo 13.5%).

The use of tiotropium in 107 patients with inadequately controlled severe asthma was evaluated in a randomized, double-blind, placebo-controlled crossover study.⁶⁰ Patients, who were currently on high-dose ICS and LABA, were randomized to receive tiotropium 5 mcg by Respimat, tiotropium 10 mcg by Respimat, or placebo in a cross-over fashion. The primary endpoint was peak FEV1 at the end of each treatment phase. Tiotropium significantly improved peak FEV1 (5 mcg: difference 139 mL; 95% CI 96-181; $p < 0.01$)(10 mcg: difference 170 mL; 95% CI 128-213; $p < 0.01$) compared with placebo. As with the previous study, the primary endpoint only considered surrogate markers of lung function, rather than reduction in asthma symptoms, exacerbations or asthma-free days.

In two replicate RCTs, a total of 912 patients with poorly controlled asthma who were receiving ICS and LABAs, were randomized to receive tiotropium (5 mcg via Respimat) or placebo for 48 weeks.⁶¹ Primary outcomes were changes in peak FEV1, trough FEV1 and time to first severe asthma exacerbation. At 24 weeks, the mean change in peak FEV1 was greater with tiotropium than with placebo: difference of 86 ± 34 mL in trial 1 ($p = 0.01$) and 154 ± 32 mL in trial 2 ($p < 0.001$). The trough FEV1 also improved with tiotropium compared with placebo. The time to the first severe exacerbation was greater with the addition of tiotropium (282 days vs. 226 days), with an overall reduction of 21% in the risk of a severe exacerbation (HR 0.79; $p = 0.03$).

Summary

There is accumulating evidence that tiotropium added to standard therapy in patients with uncontrolled moderate to severe asthma may improve lung function, as measured by PEF and FEV1. However, to date, quality of life improvements have not been measured in any of the studies. In only one study,

tiotropium reduced the risk of a severe exacerbation when compared to placebo. Further clinical trials are needed prior to recommending the addition of a LAMA for patients with inadequately controlled moderate to severe asthma. As well, it should be noted that tiotropium is not officially indicated for the treatment of asthma in Canada.

Use of LAMAs in patients with renal dysfunction

All of the currently available anticholinergics are water-soluble agents and have limited penetration across biological membranes, including the blood-brain barrier.⁶² Systemically absorbed tiotropium is mainly renally eliminated; renal impairment may affect its elimination and its safety profile. Acclidinium is rapidly metabolized by plasma esterases, resulting in low maximum plasma concentration and low systemic absorption. Systemically-absorbed acclidinium is eliminated in urine and feces; renal and liver clearances play minor roles in the total clearance of acclidinium from plasma and dose adjustment is not needed.⁶² Systemically available glycopyrronium is predominantly cleared (60-70%) from the plasma via renal elimination of the parent drug; other elimination routes include metabolism and biliary clearance.⁶³

Exhibit 14: Comparison of LAMAs^{62;64}

	Tiotropium	Acclidinium	Glycopyrronium ⁶⁵	Umeclidinium
Duration of action	24+ hrs	12 hrs	24+ hrs	24+ hrs
Dosage adjustment in renal impairment	Moderate to severe renal impairment: monitor patients closely	No dose adjustments	Severe renal impairment: caution	No dose adjustments
Dosing frequency	Once daily	Twice daily	Once daily	Once daily

Summary

Tiotropium, glycopyrronium and umeclidinium are administered once daily; acclidinium is administered twice daily. In patients with renal failure, no dose adjustments are needed with acclidinium or umeclidinium. However, for tiotropium, patients with moderate to severe renal impairment should be monitored closely. In patients with severe renal impairment, glycopyrronium should only be used if the expected benefit outweighs the potential risk.

Health Canada Alerts and Warnings

- No Health Canada advisories have been issued for tiotropium, glycopyrronium, umeclidinium or acclidinium.

Discussion

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

Availability in Canada

- In Canada, there are three single LAMA products available: tiotropium (Spiriva), glycopyrronium bromide (Seebri Breezhaler) and aclidinium (Tudorza). Another single LAMA, umeclidinium (Incruse Ellipta) has been approved by Health Canada for the management of patients with COPD but is not yet marketed. There are two LAMA+LABA combination products for the management of patients with COPD that will be introduced onto the Canadian market in 2014: indacaterol + glycopyrronium (Ultibro) and vilanterol + umeclidinium (Anoro Ellipta).
- All products are available as dry powder inhalers.
- No generic formulation is available for any of these products.
- The cost of a one-month supply for single entity LAMA products ranges from approximately \$53 (Seebri Breezhaler) to \$68 (Tudorza).

Public Plan Listing in Ontario

- In Ontario, tiotropium (Spiriva) and glycopyrronium bromide (Seebri Breezhaler) are available as general benefit listing.

Public Plan Listing in Canada

- Single-entity LAMA products are available as benefits on public drug programs across Canada.
- Tiotropium and Glycopyrronium:
 - General benefits without restrictions: Alberta, Ontario, Quebec
 - Restricted (enforced): British Columbia, Saskatchewan, Manitoba, Nova Scotia, New Brunswick, Prince Edward Island*, Newfoundland*, NIHB/NT/NU, Yukon
 *Glycopyrronium is not listed in PEI or Newfoundland.
- Aclidinium is available as a general benefit in Quebec, but not currently in any other province.
- Restriction criteria vary among the public drug plans including spirometry results for confirmation of COPD (2 plans), prior use of SABA and/or SAMA (7 plans) OR if no trial of short-acting agents, then spirometry results (4 plans).

Selected International Jurisdictions

- LAMA products were available as preferred drugs (i.e., on formulary) through all surveyed third-party payers, including managed care organizations.
- In the United States, most health plans list Spiriva as preferred LAMA on their formularies with Tudorza as non-preferred. Anoro Ellipta is currently being reviewed by many drug plans, and as such, is not yet listed.
- In Australia, the Pharmaceutical Benefits Scheme restricts LAMA products to patients with COPD. In New Zealand, Spiriva is available under Special Authority through PHARMAC (Pharmaceutical Management Agency).

Part B: Guidelines for the management of patients with COPD

- Five guidelines were reviewed: Canadian Thoracic Society (2008), Global Initiative for Chronic Obstructive Lung Disease (2014), Institute for Clinical Systems Improvement (2013), NICE Guidance for COPD (2011) and American College of Physicians, American College of Chest Physicians, American Thoracic Society and the European Respiratory Society (2011).
- All guidelines recommend the use of a LAMA or a LABA product for patients with mild to moderate COPD.
- Use of a LAMA and a LABA in combination is only recommended in 2 guidelines: Canadian Thoracic Guideline and the GOLD guidelines.
- Triple therapy (LAMA, ICS + LABA) is recommended in all guidelines for patients with severe COPD.

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

- Based on the limited data available for cost-sharing options for inhaled medications used for COPD and asthma, increasing the amount that a patient is required to pay for a medication, either through higher deductibles or via co-insurance, may result in patients being less likely to initiate or continue treatment with an inhaled medication.
- One study from British Columbia suggests that the implementation of a prior authorization process for tiotropium was associated with an increase in emergency admissions for COPD, despite an increase in use of tiotropium.

Part D: Rapid Reviews of Selected Topics

- *Comparison of dry powder inhalers:* All LAMA and LAMA+LABA products are available in Canada as dry powder inhalers. However, there are several types of DPIS on the market including single-unit devices (e.g., Handihaler, Breezhaler) and multi-dose units (e.g., Genuair, Ellipta). 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.
- *LAMAs in treatment of asthma:* There is accumulating evidence that tiotropium added to standard therapy in patients with uncontrolled moderate to severe asthma may improve lung function, as measured by PEF and FEV1. However, to date, quality of life improvements have not been measured in any of the studies. In only one study, tiotropium reduced the risk of a severe exacerbation when compared to placebo. Further clinical trials are needed prior to recommending the addition of a LAMA for patients with inadequately controlled moderate to severe asthma.
- *Use in patients with renal dysfunction:* Tiotropium, glycopyrronium and umeclidinium are administered once daily; aclidinium is administered twice daily. In patients with renal failure, no dose adjustments are needed with aclidinium or umeclidinium. However, for tiotropium, patients with moderate to severe renal impairment should be monitored closely. In patients with severe renal impairment, glycopyrronium should only be used if the expected benefit outweighs the potential risk.

Health Equity

In Ontario, LAMA single entity products (namely tiotropium and glycopyrronium) are available as a general benefit for the treatment of patients with COPD. No health equity issue was identified.

Conclusion

LAMA products (namely tiotropium and glycopyrronium) are available as general benefit currently in Ontario for the management of patients with COPD. There are two new combination products (LAMA+LABA: Ultibro and Anoro Ellipta) that are expected to be marketed in Canada in Q3.

Most public drug plans in Canada require special authorization prior to funding of these drugs for patients with COPD. Some international jurisdictions (e.g., New Zealand) restrict the use of these products via a special authorization process. However, there is a lack of literature assessing these more restrictive reimbursement schemes for adherence or outcome measures (e.g., exacerbation rates, hospitalization).

Reference List

- (1) Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. *Lancet* 2012; 379:1341-1351.
- (2) World Health Organization. Chronic obstructive pulmonary disease (COPD). <http://www.who.int/respiratory/copd/en/> [2014
- (3) Public Health Agency of Canada. Fast facts about Chronic OBstructive Pulmonary Disease (COPD) 2011. <http://www.phac-aspc.gc.ca/cd-mc/publications/copd-mpoc/ff-rr-2011-eng.php> [2012
- (4) Buist A, McBurnie M, Vollmer W, et al. BOLD Collaborative Research Group. International variation in the prevalence of COPD: a population-based prevalence study. *Lancet* 2007; 370:741-750.
- (5) Gershon AS, Guan J, Victor JC, Goldstein R, To T. Quantifying health services use for chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; 187(6):596-601.
- (6) Gershon A, Wang C, Wilton A, et al. Trends in chronic obstructive pulmonary disease prevalence, incidence and mortality in Ontario, Canada 1996 to 2007. *Arch Intern Med* 2010; 170:560-565.
- (7) Hvidsten S, Storesund L, Wentzel-Larsen T, et al. Prevalence and predictors of undiagnosed chronic obstructive pulmonary disease in a Norwegian adult general population. *Clin Respir J* 2010; 4:13-21.
- (8) Statistics Canada. Chronic obstructive pulmonary disease in Canadians, 2009 to 2011. <http://www.statcan.gc.ca/pub/82-625-x/2012001/article/11709-eng.htm> [2013
- (9) Canadian Thoracic Society. The human and economic burden of COPD: a leading cause of hospital admission in Canada. www.lung.ca [2012
- (10) Canadian Institute for Health Information. All-cause readmission to acute care and return to the emergency department. <https://secure.cihi.ca/estore/productSeries.htm?pc=PCC642> [2012
- (11) Chapman KR, Mannino DM, Soriano JB, Vermeire PA, Buist AS, Thun MJ et al. Epidemiology and costs of chronic obstructive pulmonary disease. *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology* 2006; 27(1):188-207.
- (12) Najafzadeh M, Marra CA, Lynd LD, Sadatsafavi M, Fitzgerald JM, McManus B et al. Future impact of various interventions on the burden of COPD in Canada: a dynamic population model. *PLoS One* 2012; 7(10):e46746.
- (13) Joshi M, Joshi A, Bartter T. Symptom burden in chronic obstructive pulmonary disease and cancer. *Current opinion in pulmonary medicine* 2012; 18:97-103.
- (14) Walke L, Gallo W, Tinetti M, et al. The burden of symptoms among community-dwelling older

- persons with advanced chronic disease. *Arch Intern Med* 2004; 164:2321-2324.
- (15) GlaxoSmithKline. Advair Diskus, Advair. Product Monograph [2013
 - (16) AstraZeneca Canada. Symbicort Turbuhaler. Product Monograph [2012
 - (17) Merck Canada. Zenhale. Product Monograph [2012
 - (18) Illinois Department of Healthcare and Family Services. Preferred Drug List: Illinois Medicaid. <http://www2.illinois.gov/hfs/sitecollectiondocuments/pdl.pdf> [2014
 - (19) Ovsag K, Hydery S, Mousa S. Preferred drug lists: potential impact on healthcare economics. *Vascular health and risk management* 2008; 4:403-413.
 - (20) Motheral B, Fairman K. Effect of a three-tier prescription copay on pharmaceutical and other medical utilization. *Med Care* 2001; 39:1293-1304.
 - (21) Australian Government Department of Health. Pharmaceutical Benefits Scheme. Australian Government Department of Health [2013 Available from:
URL:<http://www.pbs.gov.au/browse/body-system>
 - (22) PHARMAC. PHARMAC: Pharmaceutical Management Agency for New Zealand. <http://www.pharmac.health.nz/> [2014
 - (23) Scottish Medicines Consortium. SMC Advice Directory. http://www.scottishmedicines.org.uk/SMC_Advice/Advice_Directory/SMC_Advice_Directory?ds=Y&searchtext=symbicort&category=&submissionType=&fromDate=From%3A&toDate=To%3A&acceptedForUseCheck=Y&acceptedForRestrictedUseCheck=Y¬RecommendedForUseCheck=Y [2013
 - (24) Scottish Medicines Consortium. Tiotropium 2.5 mcg respimat inhaler. http://www.scottishmedicines.org.uk/files/tiotropium_respimat_inhaler__Spiriva-Respimat__Abbreviated_FINAL_Nov_2007_for_website.pdf [2007
 - (25) O'Donnell D, Hernandez P, Kaplan A, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease-2008 update-highlights for primary care. *Can Respir J* 2008; 15 (suppl a).
 - (26) Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: updated 2014. <http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html> . 2014.
 - (27) Institute for Clinical Systems Improvement. Diagnosis and management of chronic obstructive pulmonary disease (COPD). *ICSI, Health Care Guideline* 2011; http://www.icsi.org/guidelines_and_more/gl_os_prot/respiratory/chronic_obstructive_pulmonary_disease/chronic_obstructive_pulmonary_disease__guideline_.html.
 - (28) Anderson B, Conner K, Dunn C, et al. Institute for Clinical Systems Improvement. Diagnosis and management of chronic obstructive pulmonary disease (COPD) (updated March 2013).

https://www.icsi.org/guidelines__more/catalog_guidelines_and_more/catalog_guidelines/catalog_respiratory_guidelines/copd/ . 2013.

- (29) NICE. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. *NICE clinical guideline CG101* 2011; <http://guidance.nice.org.uk/CG101>.
- (30) Qaseem A, Wilt T, Weinberger S, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society and European Respiratory Society. *Ann Intern Med* 2011; 155:179-191.
- (31) Criner G, Bourbeau J, Diekepermer R, et al. Prevention of acute exacerbations of chronic obstructive pulmonary disease: American College of Chest Physicians and Canadian Thoracic Society Guideline. *Chest* 2014; <http://journal.publications.chestnet.org/data/Journals/CHEST/0/chest.14-1676.pdf>.
- (32) Zare H, Anderson G. Trends in cost sharing among selected high income countries: 2000-2010. *Health Polcy* 2013; 112:35-44.
- (33) Dormuth C, GLynn R, Neumann P, et al. Impact of two sequential drug cost-sharing policies on the use of inhaled medications in older patients with chronic obstructive pulmonary disease or asthma. *Clinical therapeutics* 2006; 28:964-978.
- (34) Dormuth C, Maclure M, GLynn R, et al. Emergency hospital admissions after income-based deductibles and prescription copayments in older users of inhaled medications. *Clinical therapeutics* 2008; 30:1038-1050.
- (35) Dormuth CR, Morrow RL, Carney G. Trends in health care utilization in British Columbia following public coverage for tiotropium. *Value Health* 2011; 14(4):600-606.
- (36) Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL et al. Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest* 2005; 127(1):335-371.
- (37) Taffet G, Donohue J, Altman P. Considerations for managing chronic obstructive pulmonary disease in the elderly. *Clinical interventions in aging* 2013; 9:23-30.
- (38) Sims MW. Aerosol therapy for obstructive lung diseases: device selection and practice management issues. *Chest* 2011; 140(3):781-788.
- (39) Salvi S, Gogtay J, Aggarwal B. Use of breath-actuated inhalers in patients with asthma and C. *Expert Rev Respir Med* 2014; 8(1):89-99.
- (40) Geller D. Comparing clinical features of the nebulizer, metered-dose inhaler and dry powder inhaler. *Respiratory care* 2005; 50:1313-1321.

- (41) Dolovich M, Dhand R. Aerosol drug delivery: developments in device design and clinical use. *Lancet* 2011; 377.
- (42) Wieshammer S, Dreyhaupt J. Dry powder inhalers: which factors determine the frequency of handling errors? *Respiration* 2008; 75(1):18-25.
- (43) Melani A, Bonavia V, Cilenti C, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respiratory medicine* 2011; 105:930-938.
- (44) Rau JL. Practical problems with aerosol therapy in COPD. *Respiratory care* 2006; 51(2):158-172.
- (45) Fink JB, Colice GL, Hodder R. Inhaler devices for patients with COPD. *COPD* 2013; 10(4):523-535.
- (46) Chrystyn H. The Diskus: a review of its position among dry powder inhaler devices. *Int J Clin Pract* 2007; 61:1022-1036.
- (47) Chrystyn H, Niederlaender C. The Genuair inhaler: a novel, multidose dry powder inhaler. *Int J Clin Pract* 2012; 66:309-317.
- (48) Barrons R, Pegram A, Borries A. Inhaler device selection: special considerations in elderly patients with chronic obstructive pulmonary disease. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists* 2011; 68:1221-1232.
- (49) Anderson P. Patient preference for and satisfaction with inhaler devices. *Eur Respir Rev* 2005; 14:109-116.
- (50) Chrystyn H, Small M, Milligan G, Higgins V, Gil EG, Estruch J. Impact of patients' satisfaction with their inhalers on treatment compliance and health status in COPD. *Respiratory medicine* 2014; 108(2):358-365.
- (51) van der Pale, van der Valk P, Goosens M, et al. A randomised cross-over trial investigating the ease of use and preference of two dry powder inhalers in patients with asthma or chronic obstructive pulmonary disease. *Expert Opin Drug Deliv* 2013; 10:1171-1178.
- (52) van der Palen J, Ginko T, Kroker A, et al. Preference, satisfaction and errors with two dry powder inhalers in patients with COPD. *Expert Opin Drug Deliv* 2013; 10:1023-1031.
- (53) Chapman K, Fogarty C, Peckitt C, et al. Delivery characteristics and patients' handling of two single-dose dry-powder inhalers used in COPD. *Int J COPD* 2011; 6:353-363.
- (54) Westby M, Benson M, Gibson PG. Anticholinergic agents for chronic asthma in adults. *Cochrane Database Syst Rev* 2004; 3.
- (55) Lougheed M, Lemiere C, Ducharme F, et al. Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults. *Can Respir J* 2012; 19:127-164.
- (56) Adams KS, Lowe DK. Tiotropium for adults with inadequately controlled persistent asthma. *Ann*

Pharmacother 2013; 47(1):117-123.

- (57) Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010; 363(18):1715-1726.
- (58) Peters SP, Bleecker ER, Kunselman SJ, Icitovic N, Moore WC, Pascual R et al. Predictors of response to tiotropium versus salmeterol in asthmatic adults. *J Allergy Clin Immunol* 2013; 132(5):1068-1074.
- (59) Bateman E, Kormann O, Schmidt P, et al. Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. *J Allergy Clin Immunol* 2011; 128:315-322.
- (60) Kerstjens HA, Disse B, Schroder-Babo W, Bantje TA, Gahlemann M, Sigmund R et al. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. *J Allergy Clin Immunol* 2011; 128(2):308-314.
- (61) Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med* 2012; 367(13):1198-1207.
- (62) Sharafkhaneh A, Majid H, Gross NJ. Safety and tolerability of inhalational anticholinergics in COPD. *Drug Healthc Patient Saf* 2013; 5:49-55.
- (63) Carter N. Inhaled glycopyrronium bromide: a review of its use in patients with moderate to severe chronic obstructive pulmonary disease. *Drugs* 2013; 73:741-753.
- (64) Oba Y, Zaza T, Thameem D. Safety, tolerability and risk benefit analysis of tiotropium in COPD. *Int J COPD* 2008; 3:575-584.
- (65) Anon. Glycopyrronium for COPD. *Drug and therapeutics bulletin* 2013; 51:66-68.
- (66) British Columbia Ministry of Health Services. Pharmacare Formulary Search. <http://www.health.gov.bc.ca/pharmacare/benefitslookup/faces/SearchResults.jsp> . 2014.
- (67) Drug Plan and Extended Benefits Branch. Saskatchewan Online Formulary Database. <http://formulary.drugplan.health.gov.sk.ca/> 2013
- (68) New Brunswick Department of Health. New Brunswick Prescription Drug Program Formulary. <http://www.gnb.ca/0212/nbpdpformulary-e.asp> 2013
- (69) Nova Scotia Pharmacare. Nova Scotia Formulary. <http://novascotia.ca/dhw/pharmacare/formulary.asp> 2013
- (70) PEI Pharmacare. Formulary. <http://healthpei.ca/formulary> 2013
- (71) Newfoundland and Labrador Department of Health and Community Services. Newfoundland and Labrador Interchangeable Drug Products Formulary. <http://www.health.gov.nl>

ca/health/nlmdp/fmlsearch.asp 2013

Appendix A: CDEC Recommendation for indacaterol/glycopyrronium (Ultibro Breezhaler)

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that indacaterol maleate/glycopyrronium bromide (IND/GLY) be listed for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), if the following clinical criteria are met:

Clinical Criteria:

- Moderate to severe COPD, as defined by spirometry.
- Inadequate response to a long-acting bronchodilator (long-acting beta-2 agonist [LABA] or long-acting anticholinergic [LAAC]).

Reasons for the Recommendation:

1. Two randomized controlled trials (RCTs) demonstrated that IND/GLY was similar or statistically superior to a combination of formoterol and tiotropium (FOR + TIO) (QUANTIFY; N = 934) and a combination of fluticasone propionate/salmeterol (FP/SAL) (ILLUMINATE; N = 523) for improving forced expiratory volume in one second (FEV1), quality of life, and dyspnea in patients with moderate to severe COPD.

2. At the submitted price (\$2.68 per day), the IND/GLY combination product is less costly than the following comparators: IND + GLY used separately (\$3.32 per day); FOR + TIO (\$3.66 per day); FP/SAL (\$3.25 to \$4.61 per day); all currently available LABA + LAAC combinations (range: \$3.26 to \$4.04 per day); and all currently available inhaled corticosteroid (ICS)/LABA combination products (range: \$2.76 to \$4.61 per day).

Of Note:

CDEC noted that the listing status of LABA and LAAC products varies across the drug plans participating in the CADTH Common Drug Review (CDR).

Appendix B: Single entity long-acting beta-agonists (LABAs) available in Canada

Drug	Brand Name	Manufacturer	Indication	DIN	Product availability	Cost (\$) for 30 days*
Salmeterol	Serevent	GSK	Asthma COPD	02214261	50 mcg (60DS)	59.19
				02231129	50 mcg (60DS)	59.19
Formoterol	Foradil	Novartis	Asthma COPD	02230898	12 mcg (60DS)	53.31
	Oxeze	Astra Zeneca	Asthma Exercise-induced broncho- constriction	02237224 02237225	12mcg (60DS) 6mcg (60DS)	35.51 47.27
Indacaterol	Onbrez Breezhaler	Novartis	COPD	02376938	75 mcg (30DS)	49.06

Prices obtained from McKesson January 16, 2014

Appendix C: Public drug plan benefit listings for single entity long-acting beta-2 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 (Limited Use)

BEN=unrestricted listing

Ontario Limited Use Criteria

Indacaterol

CODE 443:

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

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

Salmeterol

CODE 132:

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

CODE 391:

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

Formoterol

CODE 132:

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

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

Province	Criteria
British Columbia ⁶⁶	<p><i>Salmeterol</i></p> <ol style="list-style-type: none"> 1. Diagnosis of asthma PLUS inadequate response on optimal dose of inhaled corticosteroid OR 2. Diagnosis of COPD PLUS inadequate response on optimal short-acting beta-agonist therapy <p><i>Formoterol</i></p> <ol style="list-style-type: none"> 1. Diganosis of asthma PLUS inadequate response on optimal dose of inhaled corticosteroid <p><i>Indacaterol</i></p> <ol style="list-style-type: none"> 1. Diagnosis of COPD AND inadequate response to optimal short-acting beta-agonist therapy AND dosage does not exceed 75 mcg per day
Saskatchewan ⁶⁷	<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 food unresponsive to short-acting beta agonists or short-acting anticholinergic bronchodilators
Ontario	<p>Indacaterol: LU CODE 443</p> <p>For patients with moderate to severe COPD with persistent respiratory symptoms despite an adequate trial of, or an intolerance to, a regularly scheduled short-acting bronchodilator AND a long-acting anticholinergic.</p> <p>Note: The dose of Onbrez Breezhaler should not exceed 75mcg per day</p> <p>Salmeterol, formoterol: LU CODE 132</p> <p>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</p> <p>For patients with moderate to severe COPD with persistent respiratory symptoms despite an adequate trial of, or an intolerance to, a regularly scheduled short-acting bronchodilator AND a long-acting anticholinergic.</p>

<p>New Brunswick⁶⁸</p>	<p><i>Formoterol, salmeterol, Indacaterol</i></p> <p><u>Chronic Obstructive Pulmonary Disease</u></p> <p>For the treatment of chronic obstructive pulmonary disease (COPD) if:</p> <ul style="list-style-type: none"> • symptoms persist after 2-3 months of short-acting bronchodilator therapy (i.e. salbutamol at a maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day) • For indacaterol only: dose not to exceed 75 mcg/day <p>Coverage can be provided without a trial of short-acting agent if:</p> <ul style="list-style-type: none"> • there is spirometric evidence of at least moderate to severe airflow obstruction (FEV1 < 60% and FEV1 /FVC ratio < 0.7) and significant symptoms i.e. MRC score of 3-5**. <p>Combination therapy with tiotropium AND a long-acting beta2-adrenergic agonist/inhaled corticosteroid (LABA/ICS) will only be considered if:</p> <ul style="list-style-type: none"> • there is spirometric evidence of at least moderate to severe airflow obstruction (FEV1 < 60% and FEV1/FVC ratio < 0.7), and significant symptoms i.e., MRC score of 3-5** AND • there is evidence of one or more moderate-to-severe exacerbations per year, on average, for 2 consecutive years requiring antibiotics and/or systemic (oral or intravenous) corticosteroids. <p>NOTE: If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e. MRC scale). Spirometry reports from any point in time will be accepted.</p> <p>**Medical Research Council (MRC) Dyspnea Scale * Canadian Thoracic Society COPD Classification By Symptom/Disability: Moderate - (MRC 3-4): Shortness of breath from COPD causing the patient to stop after walking about 100 meters (or after a few minutes) on the level. Severe - (MRC 5) Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure. MRC= Medical Research Council Dyspnea Scale</p> <p><i>Formoterol, salmeterol</i></p> <p><u>Reversible obstructive airway disease</u></p> <p>For the treatment of patients, 12 years of age or older, with reversible obstructive airway disease who are using optimal corticosteroid treatment, but are still poorly controlled.</p>
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<p>Nova Scotia⁶⁹</p>	<p><i>Long-acting Beta2-agonists (i.e., Formoterol, Salmeterol, Indacaterol)</i></p> <p><u>Asthma</u></p> <ul style="list-style-type: none"> • for the treatment of moderate to severe asthma in patients who: <ul style="list-style-type: none"> ○ are compliant with inhaled corticosteroids at optimal doses; and ○ require additional symptom control, (e.g., cough, awakening at night, missing activities such as school, work or social activities because of asthma symptoms); and ○ require increasing amounts of short-acting beta2-agonists, indicative of poor control <p><u>Chronic Obstructive Pulmonary Disease</u></p> <ul style="list-style-type: none"> • for the treatment of chronic obstructive pulmonary disease (COPD), if symptoms persist after 2-3 months of short-acting bronchodilator therapy (i.e., salbutamol at a maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day) • coverage can be provided without a trial of short-acting agent if: <ul style="list-style-type: none"> ○ there is spirometric evidence of at least moderate to severe airflow obstruction, (i.e., postbronchodilator values FEV1 < 60% and FEV1/FVC ratio < 0.7), and significant symptoms (i.e., MRC score of 3-5*) • combination therapy with tiotropium and a long-acting beta2 agonist/inhaled corticosteroid will only be considered if: <ul style="list-style-type: none"> ○ there is spirometric evidence of at least moderate to severe airflow obstruction (postbronchodilator values FEV1 < 60% and FEV1/FVC ratio < 0.7), and significant symptoms (i.e., MRC score of 3-5*) <i>and</i> ○ there is evidence of one or more moderate-to-severe exacerbations per year, on average, for 2 consecutive years requiring antibiotics and/or systemic (oral or intravenous) corticosteroids <p><i>NOTE:</i> Coverage of combination therapy with tiotropium and a long-acting beta2 agonist (without an inhaled corticosteroid) will not be considered due to insufficient evidence to support substantial benefit. If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e., MRC scale). Spirometry reports from any point in time will be accepted.</p> <p>* Canadian Thoracic Society COPD Classification By Symptom/Disability: Moderate - (MRC 3-4): Shortness of breath from COPD causing the patient to stop after walking about 100 meters (or after a few minutes) on the level. Severe - (MRC 5) Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure. MRC= Medical Research Council Dyspnea Scale</p>
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PEI ⁷⁰	<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>

<p>Newfoundland⁷¹</p>	<p><i>Salmeterol, formoterol</i></p> <p><u>Reversible Obstructive Airway Disease:</u></p> <ul style="list-style-type: none"> For the treatment of reversible obstructive airway disease where optimal doses of inhaled steroids* are being used and breakthrough symptoms require frequent use of inhaled short-acting bronchodilators. <p>*Optimal defined as: >400mcg/day budesonide >250mcg/day HFA- beclomethasone >250mcg/day fluticasone</p> <p><i>Salmeterol, formoterol, indacaterol</i></p> <p><u>COPD:</u></p> <ul style="list-style-type: none"> For the treatment of chronic obstructive pulmonary disease (COPD), if symptoms persists after 2-3 months of short-acting bronchodilator therapy (i.e. salbutamol at maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day). Coverage can be approved without a trial of a short-acting agent if: <ul style="list-style-type: none"> There is spirometric evidence of at least moderate to severe airflow obstruction, i.e. FEV1 < 60% AND FEV1/FVC ratio < 0.7, and significant symptoms i.e. MRC score 3-5.* For indacaterol: coverage will be limited to a maximum dose of 75 mcg once daily. <p>Coverage of combination therapy with tiotropium and a long-acting beta2 agonist (without an inhaled corticosteroid) will not be considered due to insufficient evidence to support substantial benefit.</p> <p>If spirometry cannot be obtained, reasons must be clearly explained and other evidence regarding severity of condition must be provided for consideration (i.e. MRC scale).</p> <p>* Canadian Thoracic Society COPD Classification By Symptom/Disability: Moderate - (MRC 3-4): Shortness of breath from COPD causing the patient to stop after walking about 100 meters (or after a few minutes) on the level. Severe - (MRC 5) Shortness of breath from COPD resulting in the patient being too breathless to leave the house or breathless after undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure. MRC= Medical Research Council Dyspnea Scale</p>
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Appendix E: Webpages for Provincial Drug Formularies

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

Appendix F: Restriction Criteria for LAMA products in Canada

Province	Criteria
British Columbia	<p><i>Tiotropium, glycopyrronium, aclidinium</i></p> <p>Diagnosis of COPD where spirometry measures are: FEV₁ as a percentage of predicted value (less than or equal to 65%) AND Ratio of actual FEV₁/ FVC (less than 0.7) PLUS Inadequate response after 3 month trial of ipratropium at a dose of 12 puffs daily</p> <p>Practitioner Exemptions: Respiriologists Special Notes: In remote areas, where spirometry access is limited, spirometry measurements to be provided within 6 months.</p>
Saskatchewan⁶⁷	<p><i>Tiotropium, glycopyrronium, aclidinium</i></p> <p>(a) For treatment of COPD in patients unresponsive to short-acting beta agonists or short-acting anticholinergic bronchodilators, or (b) For treatment of moderate to severe COPD (i.e. Medical Research Council (MRC) dyspnea scale score 3 to 5), in conjunction with spirometry demonstrating moderate to severe airflow obstruction (i.e. FEV₁ <60% and low FEV₁/FVC <0.7), without a trial of short-acting agents.</p>
Manitoba	<p><i>Tiotropium, glycopyrronium</i></p> <p>For patients with moderate to severe COPD who remain symptomatic despite an adequate trial (3 months) of ipratropium.</p>
Yukon	<p><i>Tiotropium, glycopyrronium, aclidinium</i></p> <p>1) For COPD, if symptoms persist after 2-3 months of short acting bronchodilator therapy (salbutamol or ipratropium at optimal doses). 2) Please provide post-bronchodilator spirometric evidence of at least moderate to severe airflow obstruction. * 3) If spirometry cannot be obtained, other evidence regarding severity of condition must be provided for consideration. * moderate to severe airflow obstruction, ie FEV₁< 65% and FEV₁/ FVC ratio < 0.7, and significant symptoms (i.e. MRC 3-5 from Canadian Thoracic Society COPD Guidelines) MRC=Medical Research Council Dyspnea Scale. Note: Coverage of combination therapy with Glycopyrronium or Tiotropium + LABA/ ICS considered for moderate to severe COPD.</p>

<p>New Brunswick⁶⁸</p>	<p><i>Tiotropium, glycopyrronium, aclidinium</i></p> <ul style="list-style-type: none"> • For the treatment of chronic obstructive pulmonary disease (COPD) with EITHER tiotropium OR glycopyrronium OR aclidinium OR a long-acting beta2-adrenergic agonist (LABA) 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 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**). • Combination therapy with tiotropium or glycopyrronium AND a long-acting beta2-adrenergic agonist/inhaled corticosteroid (LABA/ICS) will only be considered if: <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</p> <p>* Canadian Thoracic Society COPD Classification By Symptom/Disability:</p> <p>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.</p> <p>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.</p> <p>MRC= Medical Research Council Dyspnea Scale</p>
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<p>Nova Scotia⁶⁹</p>	<p><i>Tiotropium, glycopyrronium, aclidinium</i></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 OR glycopyrronium 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>
<p>PEI⁷⁰</p>	<p><i>Tiotropium, glycopyrronium, aclidinium</i> <u>Chronic Obstructive Pulmonary Disease</u></p> <ul style="list-style-type: none"> • 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>Note: The drug programs will not pay for concurrent use of Tiotropium and Ipratropium. Note: Concurrent use of Tiotropium and long acting beta2-agonists or long acting beta2-agonists/inhaled corticosteroids will only be considered in patients where FEV1 < 60% predicted AND FEV1/FVC <0.7. A copy of the spirometry report must accompany the Special Authorization.</p>
<p>NIHB</p>	<p><i>Tiotropium, glycopyrronium</i></p> <p>For patients with chronic obstructive pulmonary disease (COPD) and who:</p> <ul style="list-style-type: none"> -did not respond to a trial of ipratropium (Atrovent); OR -did not have a previous trial of ipratropium, but who have moderate to severe COPD, defined as <60% FEV1, FEV1/FVC<0.7 and MRC 3 to 5.

<p>Newfoundland⁷¹</p>	<p><i>Tiotropium (Spiriva), glycopyrronium bromide (Seebri Breezhaler), aclidinium (Tudorza)</i></p> <p>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 maximum dose of 8 puffs/day or ipratropium at maximum dose of 12 puffs/day).</p> <ul style="list-style-type: none"> • 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.* <p>Combination therapy with tiotropium or glycopyrronium and a long-acting beta2 agonist/corticosteroid (i.e. Spiriva or Seebri plus Advair or Symbicort) will only be considered if:</p> <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. * <p>AND</p> <ul style="list-style-type: none"> • 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:</p> <p>Coverage of combination therapy with tiotropium, aclidinium or glycopyrronium 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>The dose of glycopyrronium bromide should not exceed 50 mcg per day.</p> <p>*Canadian Thoracic Society COPD Classification by symptom/disability:</p> <p><u>Moderate</u> - (MRC 3-4) shortness of breath from COPD causing the patient to stop after walking about 100 meters (or after walking a few minutes) on the level</p> <p><u>Severe</u> - (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.</p> <p><i>MRC = Medical Research Council Dyspnea Scale.</i></p>
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Appendix G: Interview Questions

How long have you listed LAMAs on your provincial formulary? How are they listed (e.g., restricted, general benefit)?
Why did you decide to list LAMAs 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 LAMAs NOT funded?
Do you restrict prescribing to certain specialties (or are certain specialties exempt from restrictions)?

Appendix H: Tiered cost-sharing options

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

Adapted from:

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

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

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

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

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

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

*in patients with FEV1/FVC <0.7

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

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

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

mMRC: Modified British Medical Research Council