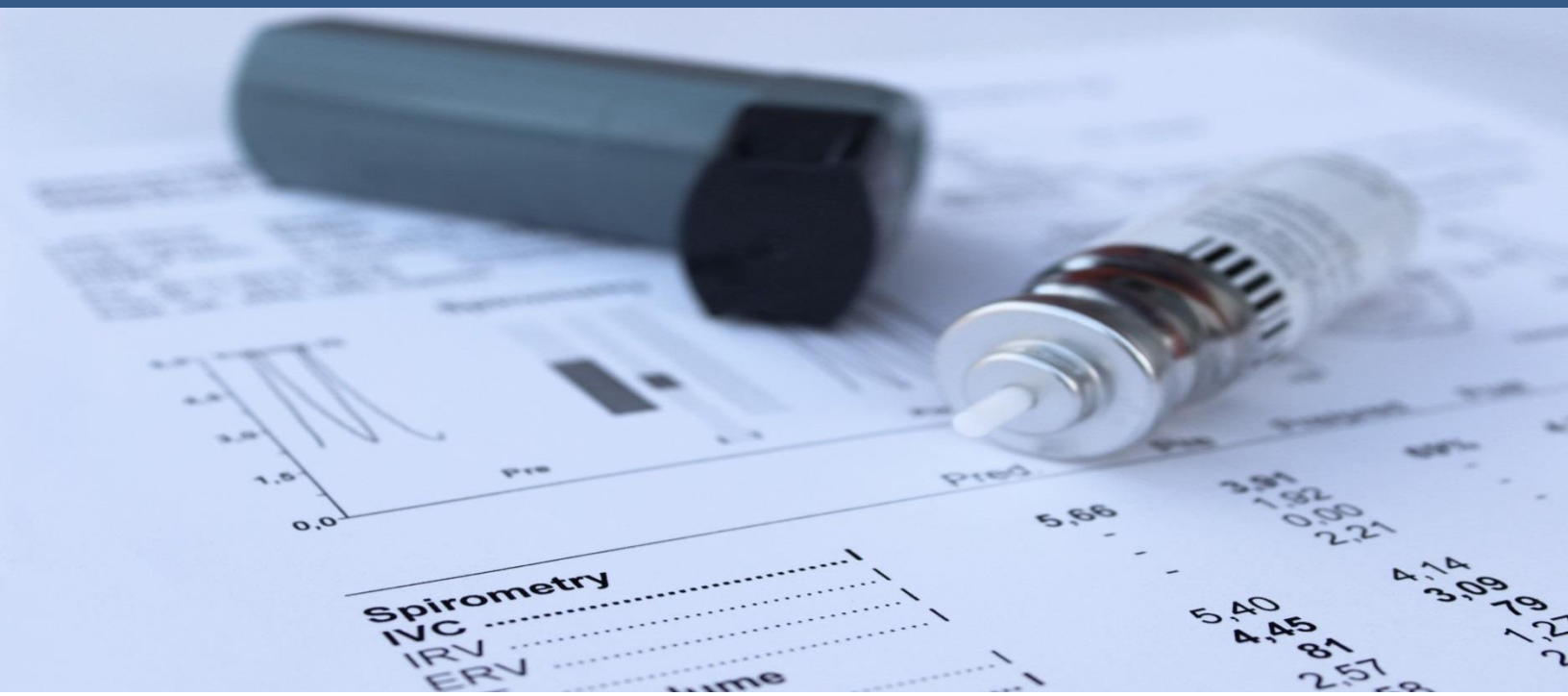
Select Drug Therapies for the Treatment of Chronic Obstructive Pulmonary Disease and Asthma



Final Reimbursement Option Recommendations

April 2015

ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Ontario Drug Policy Research Network

The Ontario Drug Policy Research Network (ODPRN) is funded to conduct drug class reviews as part of an initiative to modernize the public drug formulary in Ontario. As such, the ODPRN works closely with the Ontario Public Drug Programs (OPDP), Ministry of Health and Long-Term Care to select key priority areas and topics for formulary modernization, then conducts independent drug class reviews and disseminates the results of each of these reviews directly to the OPDP to facilitate informed decision making on public drug funding policies. The drug class reviews may lead to recommendations such as expansion of access to drugs on the formulary, revision or restriction of access to drugs, no change to current listing status and/or education of clinicians regarding appropriate prescribing.

Conflict of Interest Statement

- Muhammad Mamdani was a member of an advisory board for Hoffman La Roche, Pfizer, Novartis, GlaxoSmithKline and Eli Lilly Canada.
- Paul Oh was a member of an advisory board for Amgen, Astra Zeneca, Janssen, Novartis, Pfizer, Roche and Sanofi.
- Tara Gomes, Muhammad Mamdani and David Juurlink received grant funding from the Ministry of Health and Long-term Care.
- No other study members report any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that may present a potential conflict of interest in the ICS+LABA for COPD, ICS+LABA for asthma or LAMA for COPD Drug Class Reviews.

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Note

Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

List of Abbreviations

BFC	Budesonide + formoterol combination
COPD	Chronic obstructive pulmonary disease
EAP	Exceptional Access Program
FSC	Fluticasone propionate + salmeterol combination
ICS	Inhaled corticosteroid
ICS+LABA	ICS+LABA combination products
LABA	Long-acting beta-agonist
LAMA	Long-acting muscarinic antagonist
LU	Limited Use
MFC	Mometasone + formoterol combination
NNT	Number need to treat
ODB	Ontario Drug Benefit
ODPRN	Ontario Drug Policy Research Network
OPDP	Ontario Public Drug Programs
QALY	Quality adjusted life year
SMH	St. Michael's Hospital

Executive Summary

As part of the ODPRN's formulary modernization initiative, an evaluation of select drug therapies used in the treatment of chronic obstructive pulmonary disease (COPD) and asthma was conducted. These included:

- Inhaled corticosteroids plus long-acting beta2-agonists (ICS+LABA) combination products among patients with COPD
- Inhaled corticosteroids plus long-acting beta2-agonists (ICS+LABA) combination products among patients with asthma
- Long-acting muscarinic antagonists (LAMAs) among patients with COPD

Since ICS+LABA combination products are used for both asthma and COPD with significant overlap in the patient population, and since it would be logistically unfeasible to list differently by indication in Ontario, we have made reimbursement recommendations for these products that would apply to both asthma and COPD indications.

Key Considerations for Reimbursement Options

ICS+LABA (for asthma and COPD)

Option A: Exceptional Access Program (EAP) for All Products

- *Rationale:* Since 12-20% of the current users of ICS+LABA combination products may not have an indication of either asthma or COPD, availability of ICS+LABA products under the EAP program would limit off-label use. Nevertheless, due to the number of patients using these products currently under OPDP (approximately 164,000 patients), it is likely not feasible to place these products under the EAP program as this would place considerable strain on the system and may limit timely access to patients.

Option B: Limited Use for Asthma and COPD

- *Rationale:* Currently ICS+LABA products are listed as Limited Use for asthma only. The evidence shows that ICS+LABA combination products are efficacious and safe for patients with asthma with more severe symptoms, but would not be considered first-line therapy for most patients. Guidelines suggest use of these combination products in patients with moderate and severe COPD although our analysis suggests that ICS+LABA products are not cost-effective for patients with moderate COPD. Clinical criteria (i.e., Limited Use) will help guide physicians to the appropriate prescribing of these medications. Projected impact of expanding the Limited Use listing to patients with COPD is minimal (approximately $50,000 decrease or 0.03% of total COPD budget), as physicians currently use the LU code for asthma to access these drugs for patients with COPD.

Option C: General Benefit for All Products

- *Rationale:* ICS+LABA combination products have been shown to be efficacious and safe for treatment of asthma and COPD, although there are safety concerns regarding a potential increase

in pneumonia in patients with COPD. Guidelines suggest use of these combination products in patients with moderate and severe COPD although our analysis suggests that ICS+LABA products are not cost-effective for patients with moderate COPD. Projected impact of moving ICS+LABA products to general benefit is minimal (approximately $50,000 decrease or 0.03% of total COPD expenditures).

Option D: General Benefit (preferential listing for COPD)

- *Rationale:* For patients with COPD, evidence suggests that budesonide+formoterol (Symbicort) is more effective for decreasing risk of COPD exacerbation in patients with moderate COPD in comparison to fluticasone propionate+salmeterol (Advair); as well, fluticasone, alone or in combination with a LABA, is associated with a greater risk of pneumonia than placebo or budesonide (alone or in combination with a LABA). No comparative data is available for ICS+LABA combination products for use in patients with asthma. The potential impact of general benefit (with preferential listing) for COPD is a decrease in total respiratory expenditures of approximately 2.7% ($3.7 million).

Reimbursement Options: LAMA products

Option A: Limited Use for All Products

- *Rationale:* Currently LAMA products are listed as general benefits on the Ontario Drug Benefit formulary. These products have been shown to be effective and safe for treatment of patients with COPD. LAMA products are not indicated for treatment of asthma, although they have been studied in patients with uncontrolled moderate to severe asthma. Potential impact of moving LAMA products to Limited Use is minimal, as our utilization data show that these products are primarily used in the treatment of patients with COPD.

Option B: General Benefit for All Products

- *Rationale:* LAMA products have been shown to be effective and safe for treatment of patients with COPD. No impact on accessibility or budget is anticipated, as LAMA products are currently listed as general benefits on the Ontario Drug Benefit formulary. However there may be increased off-label use of these products among patients with asthma due to recent studies evaluating LAMAs in patients with inadequately controlled persistent asthma.

Findings from the ODPRN Citizens' Panel

Citizens' Panel members rated each of the policy options on factors related to acceptability, accessibility and affordability, and ranked options from most to least preferable from a societal viewpoint. The final rankings were as follows:

- ICS+LABA (for asthma and COPD): Limited Use was the most acceptable option, followed by General Benefit for all products
- LAMA for COPD: Limited Use was the most acceptable option, followed by General Benefit

Recommendation

After balancing access, efficacy and safety, use in appropriate indications, input from stakeholders and feedback from the ODPRN Citizens' Panel, the following reimbursement options are recommended for the Ontario Public Drug Program.

ICS+LABA (for asthma and COPD)

- Limited Use for Asthma and COPD

LAMA for COPD

- Limited Use for All Products for COPD

OR

- General Benefit for All Products

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Overview

Asthma and chronic obstructive pulmonary disease (COPD) are both chronic obstructive airway diseases although they differ in their causes and pathophysiology. Up to 25% of adult patients with obstructive airway diseases have manifestations of both diseases, termed the asthma-COPD overlap[1]. Pharmacologic treatment options for asthma and COPD include medications such as short-acting agents (e.g., short-acting beta-agonists) and long-acting agents (e.g., inhaled corticosteroids [ICSs], long-acting beta-agonists [LABAs], long-acting muscarinic antagonists [LAMAs, also known as long-acting anticholinergic agents])[2;3]. LABAs and LAMAs are inhaled bronchodilators and ICSs help to reduce airway inflammation.

Asthma and COPD affect a significant proportion of the population, and result in considerable expenditures to the Ontario Public Drug Programs (OPDP). In Ontario, approximately 12% of the population 35 years and older is diagnosed with COPD[4], and about 13% of the population is diagnosed with asthma[5]. Currently in Ontario, ICS+LABA combination products are only available on the Ontario Drug Benefit (ODB) formulary for the treatment of asthma under the Limited Use program. LAMA products are available as a general benefit on the ODB formulary (Appendix A).

As part of the formulary modernization review, ICS+LABA combination products were evaluated for the management of patients with asthma and COPD as two separate drug class reviews to provide recommendations for funding of these products in Ontario. As well, LAMAs were reviewed by ODPRN as a separate drug class review.

This report summarizes the reimbursement options for the reviewed drug classes: ICS+LABA for COPD, ICS+LABA for asthma and LAMA products for COPD, and provides final recommendations to OPDP. More detailed information for each of the reviews can be found on the ODPRN website.

Reimbursement Options for Respiratory Drug Classes

ICS+LABA

Key Considerations: ICS+LABA for COPD

Efficacy

- Overall, ICS+LABA combination products were shown to reduce exacerbation rates in patients with moderate COPD and improve lung function and quality of life. ICS+LABA products were found to be more effective for reducing exacerbations in patients with moderate COPD than other long-acting inhaled therapies for COPD, including LABAs, LAMAs and ICS products.
- When ICS+LABA products were compared with each other, the two ICS+LABA agents with the highest probability of being the most effective for decreasing risk of COPD exacerbation in patients with moderate COPD were budesonide+formoterol combination (BFC) and mometasone+formoterol combination (MFC); note that MFC is not approved in Canada for treatment of COPD. Compared to fluticasone propionate+salmeterol combination (FSC), BFC reduced exacerbations significantly in

patients with moderate COPD (number needed to treat (NNT) = 8).

Safety

- An increased risk of pneumonia has been attributed to ICS, either alone or in combination with LABA. Although no head-to-head randomized controlled trials have been done comparing BFC and FSC, observational research suggests that fluticasone propionate, alone or in combination with a LABA, is associated with a greater risk of pneumonia than placebo, budesonide (alone or in combination with a LABA) or LABA.
- For the safety outcome of arrhythmias, no statistically significant differences were observed across any of the ICS+LABA agents compared with each other, ICS alone, LABA alone, or placebo.
- The balance between the risks and benefits of ICS+LABA combination products must be carefully considered.

Accessibility

- Despite the lack of coverage of ICS+LABA products for COPD in Ontario, no accessibility issues were identified in our review. In our one-on-one interviews with respirologists and primary care physicians, it was noted that physicians often resort to using the Limited Use (LU) code 330 for asthma to access these drugs for their COPD patients.

Pharmacoeconomics

- In patients receiving ICS and LABA via separate inhalers, our de novo economic evaluation supports the cost effectiveness of moving to administration of the combination via a single inhaler. The incremental cost per quality adjusted life year (QALY) gained for ICS and LABA when compared with LABA alone was dependent on the severity of disease: $80,000 for patients with very severe COPD, $100,000 for at least severe COPD and $260,000 for at least moderate COPD. Using a QALY of $100,000, our analysis suggests that ICS+LABA products are not cost-effective for patients with moderate COPD but are cost-effective for patients with severe or very severe disease; however, clinical guidelines suggest use of these combination products in patients with moderate and severe COPD.[2;6]
- Based on our cost-effectiveness model, price reductions for ICS+LABA products needed to achieve cost-effectiveness (relative to formoterol) for patients with moderate COPD range from 26% for Symbicort to 96% for Breo Ellipta (Appendix B).

Key Considerations: ICS+LABA for asthma

Efficacy

- Our network meta-analysis found that adjustable or fixed dose combined ICS+LABA inhalers (any dose) had the greatest probability of decreasing the risk of moderate to severe exacerbations in patients with chronic asthma compared to other long-acting agents such as ICS, LABAs and leukotriene receptor antagonists. For this outcome, statistically significant results were found for ICS+LABA combination (any dose) compared to LABA (NNT 3-4).

Safety

- There were no significant differences in risk of cardiovascular disease or cardiovascular-related mortality across all treatment groups.
- Regular use of LABAs (as monotherapy) in patients with asthma has shown to lead to increased asthma mortality[7]. Meta-analyses of RCTs that have examined the safety of LABAs in combination with ICS have shown inconsistent results, although most have shown no significant differences in asthma-related mortality [8;9].

Accessibility

- In Ontario, ICS+LABAs are available on the ODB formulary as Limited Use for patients with asthma. As such, no accessibility issues for qualifying patients, including those aged 65 years and older, were identified in our review.

Pharmacoeconomics

- The de novo economic evaluation found that the later LABA was introduced into therapy, the more cost-effective the treatment strategy became. Therefore, the optimal strategy considered was introducing LABA to patients when they were uncontrolled with high doses of ICS. Note that guidelines recommend for patients 12 years of age and older who remain uncontrolled on low-dose ICS, the addition of a LABA, ideally in the form of a combination inhaler.[10]

Reimbursement Options: ICS+LABA (for asthma and COPD) (Exhibit 1)

Option A: Exceptional Access Program for All Products

- Exceptional Access Program for asthma: Fluticasone propionate+salmeterol (Advair, Advair Diskus), budesonide+formoterol (Symbicort), mometasone+formoterol (Zenhale)
- Exceptional Access Program for COPD: Fluticasone propionate+salmeterol (Advair Diskus), budesonide+formoterol (Symbicort), fluticasone furoate+vilanterol (Breo Ellipta)
- Clinical criteria: see Appendix C and D

Pros:

- Since 12-20% of the current users of ICS+LABA combination products may not have an indication of either asthma or COPD, availability of ICS+LABA products under the EAP program would limit off-label use.

Cons:

- Due to the number of patients using these products currently under OPDP (approximately 164,000 patients with approximately 25% new users every year), it is likely not feasible to place these products under the EAP program as this would place considerable strain on the system and may limit timely access to patients.

Option B: Limited Use for Asthma and COPD

- Limited Use for asthma (status quo): Fluticasone propionate+salmeterol (Advair, Advair Diskus), budesonide+formoterol (Symbicort), mometasone+formoterol (Zenhale)
- Limited Use for COPD: Fluticasone propionate+salmeterol (Advair Diskus), budesonide+formoterol (Symbicort), fluticasone furoate+vilanterol (Breo Ellipta)
- Clinical criteria: see Appendix C and D

Pros:

- Currently ICS+LABA products are listed as Limited Use for asthma only. ICS+LABA combination products have been shown to be efficacious and safe for treatment of asthma and COPD, although there are safety concerns regarding a potential increase in pneumonia among patients with COPD. Guidelines suggest use of these combination products in patients with moderate and severe COPD although our analysis suggests that ICS+LABA products may not be cost-effective for patients with moderate COPD. For patients with asthma, guidelines recommend use of ICS+LABA in patients who are uncontrolled on inhaled steroid.
- Providing coverage for all products allows choice in terms of delivery devices.
- Clinical criteria (i.e., Limited Use) will help guide physicians to the appropriate prescribing of these medications for both asthma and COPD.
- Projected impact of expanding the Limited Use listing to patients with COPD is minimal (approximately $50,000 decrease or 0.03% of *total* COPD budget), as physicians currently use the LU code for asthma to access these drugs for patients with COPD. As well, potential savings could be realized as patients on dual therapy (ICS and LABA as two inhalers) would be switched to ICS+LABA combination therapy.

Cons:

- There is the potential for increased utilization of ICS+LABA if the clinical criteria are expanded to include the indication of COPD. However, as these products are currently being used for COPD, it is expected that the increased utilization would be minimal.

Option C: General Benefit for All Products

- General Benefit: Fluticasone propionate+salmeterol (Advair, Advair Diskus), budesonide+formoterol (Symbicort), mometasone+formoterol (Zenhale), fluticasone furoate+vilanterol (Breo Ellipta)

Pros:

- ICS+LABA combination products have been shown to be efficacious and safe for treatment of asthma and COPD, although there are safety concerns regarding a potential increase in pneumonia in patients with COPD. Guidelines suggest use of these combination products in patients with moderate and severe COPD although our analysis suggests that ICS+LABA products may not be cost-effective for patients with moderate COPD. For patients with asthma, guidelines recommend use of ICS+LABA in patients who are uncontrolled on inhaled steroid.
- Projected impact of moving ICS+LABA products to general benefit is minimal (approximately $50,000 decrease or 0.03% of total COPD expenditures), given current use within LU code and depending on extent to which these agents may be used off-label for other indications.

Cons:

- Lack of clinical criteria (e.g., Limited Use criteria) may result in increase in use of ICS+LABA for non-asthma, non-COPD indications, such as chronic cough. There is little evidence that the ICS+LABA products are effective for the management of chronic cough. Although we cannot estimate the potential budget impact of this potential expansion in use, it has the possibility to be fairly considerable.

<u>Option D: General Benefit (preferential listing for COPD)</u>

- General Benefit for COPD: Budesonide+formoterol (Symbicort)
- Limited Use for asthma: Fluticasone propionate+salmeterol (Advair, Advair Diskus), budesonide+formoterol (Symbicort), mometasone+formoterol (Zenhale)
- Not Listed: Fluticasone furoate+vilanterol (Breo Ellipta)

Pros:

- For patients with COPD, evidence indicates that BFC (Symbicort) is most effective for decreasing risk of COPD exacerbation in patients with moderate COPD in comparison to fluticasone propionate+salmeterol (Advair); as well, fluticasone, alone or in combination with a LABA, is associated with a greater risk of pneumonia than placebo or budesonide (alone or in combination with a LABA). The potential impact of general benefit (with preferential listing of BFC) for COPD is a decrease in total respiratory expenditures of approximately 2.7% ($3.7 million).

Cons:

- This option cannot be considered for the indication of asthma as no comparative data is available for ICS+LABA combination products for use in patients with asthma.
- Fluticasone+salmeterol (Advair) is the most commonly used ICS+LABA product in Ontario; it may not be feasible to switch all patients currently on Advair over to Symbicort.
- Advair and Symbicort are available in two different types of inhalers. Several factors need to be considered in selecting a device including patient age and ability to use selected device correctly, as well as physician and patient preference.
- It should be noted that physicians may resort to using the Limited Use code for asthma for ICS+LABA combination products to access products not covered for COPD.

Exhibit 1: Assessment of Reimbursement Options for ICS+LABA products (for COPD and asthma)

	Option A: Exceptional Access Program for all products	Option B: Limited Use for all products	Option C: General Benefit for all products	Option D: General Benefit (preferential listing)
Efficacy	• COPD: ICS+LABA are more effective than other long-acting inhaled therapies *Exacerbations* (moderate COPD): ICS+LABA more effective than LABA, LAMA and ICS *Lung function*: ICS+LABA>LAMA=LABA>ICS[11] *Quality of life*: ICS+LABA>LAMA>LABA>ICS[11] • Asthma: ICS+LABA > LABA, LTRA, ICS for decreasing risk of exacerbation			COPD: BFC higher probability than FSC or FVC for decreasing risk of exacerbation in moderate COPD Asthma: No comparison available for ICS+LABA products
Safety concerns	• COPD: Increased risk of pneumonia with ICS (either alone or in combination with LABA) • Asthma: no significant differences in risk of cardiovascular disease or cardiovascular-related mortality across all treatment groups			COPD: Fluticasone (±LABA) greater risk for pneumonia than placebo, budesonide (±LABA), LABA Asthma: No comparison available for ICS+LABA products
Accessibility*	164,000 users (approximately 25% new users)	205,000 users	205,000 users	205,000 users
Budget Impact ‡	Not modeled	COPD: ↓0.03% ($50,693)** Asthma: status quo ($112 million)	COPD: ↓0.03% ($50,693)** Asthma: status quo ($112 million)	COPD: ↓2.7% ($4.0 million)** Asthma: not modeled
Alignment with other jurisdictions	9 of 12 (75%) public drug programs in Canada list on restricted basis	Ontario lists ICS+LABA for asthma only	Alberta and Manitoba list ICS+LABA as general benefits	No public drug program in Canada
Indication creep	Will limit use to approved indications with specific criteria	May limit use of ICS+LABA to COPD and asthma indications	No restriction on indication Note: use of ICS+LABA for non-COPD, non-asthma indications was noted in up to 12-20% of patients	

*based on 2012 usage

**only includes Advair, Advair Diskus, Zenhale and Symbicort

‡ total respiratory budget for long-acting agents: asthma $112 million (fiscal 2012), COPD $149 million (fiscal 2012)

LAMA products

Key Considerations: LAMA for COPD

Efficacy

- For exacerbations in patients with moderate COPD, LAMA products were found to be more effective than LABAs. However, individual LAMAs products were found to be inferior to ICS+LABA products.
- When LAMA products were compared to each other, no statistically significant differences were observed.

Safety

- For the safety outcome of arrhythmias, no statistically significant differences were observed across any of the LAMA comparisons.
- For the safety outcome of pneumonia, LAMAs had a lower risk of pneumonia relative to ICS+LABA, but no other differences were observed for LAMA products.

Accessibility

- LAMAs are available as a general benefit in Ontario, for ODB-eligible patients, including those 65 years and older. As such, no accessibility issues were identified in our review.

Pharmacoeconomics

- The de novo economic evaluation found that LAMA monotherapies were cost effective when compared to ICS single agents and salmeterol (Serevent), but not to formoterol (Oxeze) at the listed drug prices. Although quite limited, the available data suggested triple therapy (i.e., LAMA plus ICS+LABA) was not cost-effective compared to ICS+LABA combination therapies.

LAMA+LABA combination products

LAMA+LABA combination products are new treatment options for the management of patients with COPD: Ultibro and Anoro Ellipta were available in Canada in March 2014. Some of the evidence for the efficacy and safety of LAMA+LABA combination products was only available after our systematic review was initiated. Therefore, the results of our NMA should be considered preliminary for safety and efficacy as well as for the pharmacoeconomic analysis for LAMA+LABA combination products and no recommendations for the listing of LAMA+LABA combination products for OPDP will be made.

Reimbursement Options: LAMA products (Exhibit 2)

Option A: Limited Use for All Products

- Limited use for COPD: Tiotropium (Spiriva), glycopyrronium (Seebri Breezhaler), aclidinium (Tudorza): listed as Limited Use for COPD
- Clinical criteria: see Appendix E

Pros:

- Currently LAMA products are listed as general benefits on the Ontario Drug Benefit formulary. These products have been shown to be effective and safe for treatment of patients with COPD.
- Clinical criteria (i.e., Limited Use) may help guide physicians to the appropriate prescribing of these medications for COPD, and limit their use in asthma, where there is no current indication.
- Potential impact of moving LAMA products to Limited Use is minimal, as our utilization data show that these products are primarily used in the treatment of patients with COPD. Approximately 88% of LAMA users in 2012 in Ontario had a diagnosis of COPD, with 4% of users with a diagnosis of asthma only. However there may be increased off-label use of these products among patients with asthma due to recent studies using LAMAs in patients with inadequately controlled persistent asthma.

Cons:

- This option may be considered more "restrictive" than the currently available general benefit listing.

Option B: General Benefit for All Products

- General Benefit (status quo): Tiotropium (Spiriva), glycopyrronium (Seebri Breezhaler), aclidinium (Tudorza)

Pros:

- LAMA products have been shown to be effective and safe for treatment of patients with COPD.
- No impact on accessibility or budget is anticipated, as LAMA products are currently listed as general benefits on the Ontario Drug Benefit formulary.

Cons:

- Lack of clinical criteria (e.g., Limited Use criteria) may result in increase in use of LAMAs for non-COPD indications. Note that although LAMA products are not indicated for treatment of asthma, they have been studied in patients with uncontrolled moderate to severe asthma, and therefore there is a potential for prescribers to use these drugs outside of the COPD indication.

Exhibit 2: Assessment of Reimbursement Options for LAMA products

	Option A: Limited Use for all products	Option B: General Benefit for all products
Efficacy	Exacerbations: ICS+LABA>LAMA>LABA Lung function: ICS+LABA>LAMA=LABA>ICS Quality of life: ICS+LABA>LAMA>LABA>ICS Cost-effectiveness: based on current list prices, LAMA monotherapies were not cost effective when compared to formoterol	
Safety concerns	Pneumonia: Glycopyrronium and tiotropium had greatest probability of being safest for pneumonia CV mortality: glycopyrronium and glycopyrronium-indacterol had greatest probability of being safest	
Accessibility*	120,000 users	137,000 users
Budget Impact *	$63 million (↓12.5%)**	$72 million (status quo)
Alignment with other jurisdictions	9 of 12 public drug programs in Canada list on restricted basis (i.e., special authorization needed)	Alberta, Quebec and Ontario list as general benefit
Indication creep	May limit use of LAMAs to COPD (studies suggest that LAMAs may be efficacious in patients with asthma)	No restriction on indication (may be used for non-COPD indications such as asthma)

*Based on usage in fiscal 2012

** Crude estimate based on use of LAMAs for COPD (with or without asthma) only

Other Issues for Consideration

Coverage for Spacers

Spacers, also known as holding chambers, are placed on the mouthpiece of a metered dose inhaler to extend it away from the mouth of a patient. Compared with an MDI alone, spacers minimize coordination difficulties and reduce oropharyngeal deposition.[12] These devices should be considered for use if a patient is unable to properly use an MDI alone or if oropharyngeal or systemic effects are a problem (for example, patients on inhaled corticosteroids).[13] Currently in Canada, seven of 11 public plans provide coverage for spacer devices (1 device every 12 months). In Ontario, these products are not funded under any program.

Recommendation: Although spacers were not part of the ODPRN drug class review, additional review of these products is warranted for consideration for funding by MOHLTC.

Therapeutic Notes (LAMAs)

LAMAs are currently listed in the ODB formulary as general benefit, with a "Therapeutic Note". These notes are used to provide guidance to prescribers on where the product can be used in the most cost-effective manner, and also help define appropriate therapy. The "Therapeutic Note" for LAMAs states:

> *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).

However, the product monographs for Spiriva, Tudorza, and Seebri do NOT include age-related CNS adverse effects such as confusion, paranoia, hallucinations or memory impairment.[14-16] As well, no case reports have been published documenting these adverse effects in the elderly. Note that the inclusion of this therapeutic note is based on data from the American Hospital Formulary Service, which provides an overarching warning for all anticholinergic agents, regardless of route of administration.

Recommendation: Based on the available evidence, OPDP should consider deleting or revising this Therapeutic Note to indicate that long-acting inhaled anticholinergic agents (LAMAs) are not associated with these adverse events.

Stakeholder Review

Findings from the stakeholder review contributed to selection of final policy recommendations, and include feedback solicited from an open call for review, comments received during a workshop for stakeholders, as well as results from the ODPRN Citizen's Panel.

Findings from the ODPRN Citizens' Panel

A total of four Citizens' Panel (CP) members rated each of the policy options on factors related to acceptability, accessibility and affordability, and ranked options from most to least preferable from a societal viewpoint. Through one teleconference meeting and two rounds of an online survey, CP members voiced the following perceptions:

- ICS+LABA (for asthma and COPD): Limited Use was the most acceptable option, followed by General Benefit for all products
- LAMA for COPD: Limited Use was the most acceptable option, followed by General Benefit

With regards to reimbursement options for ICS+LABA (for asthma and COPD), the majority of members preferred options B or C (Limited Use and General Benefit, respectively), but several of them were unable to differentiate between the two. Those who preferred the Limited Use option liked the extra step doctors needed to take to prescribe the drugs, but also felt that this could potentially restrict beneficial off-label use. Those who were in favor of General Benefit felt that increased access to helpful medicine for all that need it, regardless of specific diagnosis, is a good thing. However they were concerned about the potential lack of oversight, which could lead to overprescribing. Overall, Option 2 was their first choice, Option 3 was their second choice, and Option's 1 & 4 were tied for their third, and least favorable choice.

The sentiments regarding the two options for LAMA products (Limited Use and General Benefit for all products) mirrored their opinions of ICS-LABA options. However, all members seemed to be in agreement that there did not appear to be a need to change the current reimbursement option. General Benefit allows all who could benefit from LAMAs to receive them, at no increased cost to the system.

Overall, Option 2 was the preferred choice, with Option 1 being the least favorite.

Exhibit 3: Final Ranking of Policy Options (ICS+LABA for asthma and COPD)

	Final Ranking
Option 2: Limited Use (LU) for all products	1
Option 3: General Benefit (GB) for all products	2
Option 1: Exceptional Access Program (EAP) for all products	3
Option 4: General Benefit (GB) with preferential listing for COPD only	3

Exhibit 4: Final Ranking of Policy Options LAMAs for COPD

	Final Ranking
Option 2: Limited Use (LU) for all products	1
Option 3: General Benefit (GB) for all products	2

Final Policy Recommendations and Conclusion

After balancing access, efficacy and safety, use in appropriate indications, input from stakeholders and feedback from the ODPRN Citizens' Panel, the following reimbursement options are recommended for the Ontario Public Drug Program.

ICS+LABA (for asthma and COPD)

- Limited Use for Asthma and COPD

LAMA for COPD

- Limited Use for All Products for COPD

OR

- General Benefit for All Products

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Appendix A: Ontario public plan listing of ICS+LABA, LAMA, LAMA+LABA and LABA products

	Asthma	COPD
Inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA) combination products		
Fluticasone propionate+ salmeterol (Advair Diskus, Advair)	Limited use	Not listed
Budesonide+formoterol (Symbicort)	Limited use	Not listed
Fluticasone furoate+vilanterol (BreoEllipta)	Not listed	Not listed
Mometasone+formoterol (Zenhale)	Limited use	Not listed
Long-acting muscarinic antagonists (LAMA)		
Tiotropium (Spiriva)	Not indicated for asthma	General benefit
Glycopyrronium (Seebri Breezhaler)	Not indicated for asthma	General benefit
Aclidinium (Tudorza)	Not indicated for asthma	General benefit
Long-acting beta-agonists (LABA)		
Indacaterol (Onbrez Breezhaler)	Not indicated for asthma	Limited Use
Salmeterol	Limited use	Limited use
Formoterol	Limited use	Not indicated for COPD
Long-acting muscarinic antagonists (LAMA) and long-acting beta-agonists (LABA) combination products		
Glycopyrronium + indacaterol (Ultibro)	Not indicated for asthma	Not listed
Umeclidinium + vilanterol (Anoro Ellipta)	Not indicated for asthma	Not listed

Current as of February 23, 2015.

Appendix B: Price reductions needed to achieve cost-effectiveness

Product	Patients with at least moderate COPD*	Patients with at least severe COPD*	Patients with only very severe COPD*
Symbicort	↓26%	↓12%	↓4%
Advair Diskus	↓86%	↓89%	↓92%
Breo Ellipta	↓96%	↓96%	↓98%

*Based on costs derived from the Ontario Drug Formulary (for Symbicort and Advair Diskus) or wholesale price (Breo Ellipta).

NOTE: relative to formoterol, which is optimal assuming a threshold of $50,000 QALY.

Appendix C: Criteria for Coverage for ICS+LABA for COPD (proposed)

Criteria for Coverage

- Patient with moderate to severe COPD
  AND
- History of exacerbations
  OR
- Inadequate response to LABA and LAMA

Authorization Period
Indefinite
Notes
COPD disease severity is based on spirometry, symptoms and disability.

Classification by symptoms and disability*

COPD stage	Symptoms
Mild	Shortness of breath from COPD when hurrying on the level or walking up a slight hill
Moderate	Shortness of breath from COPD causing the patient to stop after walking approximately 100m (or after a few minutes) on the level
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

Classification by impairment of lung function*

COPD stage	Spirometry (postbronchodilator) FEV1 predicted**
Mild	≥80%
Moderate	50-79%
Severe	30-49%
Very severe	<30%

*from Canadian Thoracic Society recommendations. Can Respir J 2007;14 (suppl B):5B-32B
**FEV1/FVC<0.7

Assessment of criteria for coverage for ICS+LABA for COPD

Criteria	Comments
Patient with moderate to severe COPD	Severity of COPD is measured by symptoms and disability, as well as impairment of lung function; spirometry is required for diagnosis but treatment decisions should be guided by severity of symptoms and disability ICS+LABA are recommended for patients with moderate to severe COPD and a history of exacerbations
History of exacerbations	ICS+LABA are recommended for patients with moderate to severe COPD and a history of exacerbations
Inadequate response to LABA and LAMA	LABA and LAMA products are generally recommended for patients at low risk of exacerbations but persistent symptoms. For patients who have an inadequate response to both LABA and LAMA (either alone or in combination), ICS+LABA may be an appropriate alternative.

Appendix D: Criteria for Coverage for ICS+LABA for Asthma (proposed)

Criteria for Coverage

- For the treatment of patients with asthma

AND

- Patients are using inhaled corticosteroids optimally

AND

- Patients are still experiencing breakthrough symptoms

Authorization Period

Indefinite

Assessment of criteria for coverage for ICS+LABA for asthma

Criteria	Pros
Treatment of asthma	ICS+LABA combination products have been found to be safe and effective for treatment of asthma
Patient using inhaled corticosteroid optimally	ICSs are the first-line controller therapy for patients with asthma. If patients are uncontrolled on inhaled corticosteroid and require additional therapy, addition of a LABA to ICS is recommended in patients 12 years of age and older.
Patients are still experiencing breakthrough symptoms	Asthma control is assessed by various symptoms including daytime symptoms, night-time symptoms, impact on physical activity, exacerbations, absence from work or school due to asthma, need for a short-acting beta-agonist, and spirometric measurements.

Appendix E: Criteria for Coverage for LAMA for COPD (proposed)

Criteria for Coverage

- Patient with COPD, persistent symptoms and moderate to severe airflow obstruction

Authorization Period
Indefinite

Notes
COPD disease severity is based on spirometry, symptoms and disability.

Classification by symptoms and disability*

COPD stage	Symptoms
Mild	Shortness of breath from COPD when hurrying on the level or walking up a slight hill
Moderate	Shortness of breath from COPD causing the patient to stop after walking approximately 100m (or after a few minutes) on the level
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

Classification by impairment of lung function*

COPD stage	Spirometry (postbronchodilator) FEV1 predicted**
Mild	≥80%
Moderate	50-79%
Severe	30-49%
Very severe	<30%

*from Canadian Thoracic Society recommendations. Can Respir J 2007;14 (suppl B):5B-32B
**FEV1/FVC<0.7

Assessment of criteria for coverage for LAMA for COPD

Criteria	Pros
Patient with persistent symptoms and moderate to severe airflow obstruction	• Severity of COPD is measured by symptoms and disability, as well as impairment of lung function; spirometry is required for diagnosis but treatment decisions should be guided by severity of symptoms and disability • For patients with persistent symptoms and moderate to severe airflow obstruction, LAMA or LABA is recommended.