

FINAL CENSORED REPORT

ICS+LABA Combination Products for the Treatment

Pharmacoepidemiology Report

Diana Martins, Matthew Stanbrook, Kimberly Fernandes, Zhan Yao, Samantha Singh, Mina Tadrous, Sandra Knowles, David Juurlink, Muhammad Mamdani and Tara Gomes

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 Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

Executive Summary

National and Provincial Trends in ICS+LABA Prescribing

ICS+LABA combination products are the second most commonly dispensed anti-inflammatory and bronchodilator agents in Canada, accounting for 22.4% (1.1 million prescriptions out of 4.7 million prescriptions) of all prescriptions dispensed in the fourth quarter (Q4: October to December) of 2013. Ontario has the second-highest population-adjusted utilization rate of provincially-funded ICS+LABA combination products (7,127 prescriptions dispensed per 100,000 eligible population vs. national average of 5,063 prescriptions dispensed per 100,000 eligible population in Q4 2013). The total national expenditure on ICS+LABA combination products in the last quarter of 2013 was \$129.3 million, 52.3% of overall national spending on anti-inflammatory and bronchodilator products (\$247.2 million, Q4 2013).

Use of ICS+LABA Combination Products in Ontario

Just over half of all ICS+LABA combination products dispensed in Ontario are paid for through the Ontario Public Drug Program (OPDP). In Q4 2013, 53% of prescriptions (N= 217,935) were paid for through OPDP, 38% (N= 158,027) through private health insurance, and the remainder (N=38,667; 9%) through cash payments and Non-Insured Health Benefits (NIHB). In 2012, ICS+LABA combination products were the third most commonly dispensed therapy among youth aged 12 to 17 (following SABA and ICS therapies), the second most commonly dispensed therapy among adults aged 18 to 64 (following SABA therapy) and the most commonly dispensed therapy among older adults (aged 65 years and older) public drug plan beneficiaries with asthma. Among beneficiaries with asthma, the number of ICS+LABA combination product users has increased nearly 23-fold across all age groups between 2000 and 2012. By 2012, among asthma patient beneficiaries, the majority (71%) of ICS+LABA combination products were being used by older adults. The rate of ICS+LABA combination product users has also increased over time across all age groups (between 2000 and 2013); however a decline in the rate of users among youth and young adults beneficiaries was observed between 2011 and 2013. Advair was the most utilized ICS+LABA combination therapy product and had the highest average cost per user among beneficiaries with asthma aged 12-17 (54.2% and \$362.1 respectively), 18-64 (59.7% and \$697.9, respectively) and 65 and older (60.6%; \$791.3, respectively) in 2012. Symbicort was the second most utilized combination product in 2012. By 2012, the overall cost of provincially funded ICS+LABA combination products dispensed to asthma drug plan beneficiaries in Ontario was \$79.2 million.

Characteristics of ICS+LABA Users with Asthma in Ontario in 2012

In fiscal year 2012, 111,064 asthma patients aged 12 and older received provincially-funded ICS+LABA combination products in Ontario. The majority (64.2%) of youth (aged 12-17) were new ICS+LABA users while 44.9% of young adults (aged 18-65) and 22.8% of older adults (over 65 years of age) were new users of ICS+LABA therapy. Advair (Diskus and HFA) was the most commonly used product across all age groups. Asthma patients dispensed ICS+LABA products through the OPDP were typically over 65 years of age (N=77,603; 69.9%) and lived in urban locations (N=97,528; 87.8%). The majority of asthma therapy users aged 18 and older were female (N=69,846; 62.5%) compared to about half among those younger than 18 years of age (N=476; 47.3%). A greater proportion of youth users experienced asthma

exacerbations in the previous year, compared to younger adults and older adults (10.1%, 5.8% and 2.1%, respectively). Among older adults, Advair users were more likely to be residents of long-term care facilities compared to Symbicort and Zenhale users (5.6%, 2.1% and 0.8%, respectively).

Patterns of Use and Discontinuation of Asthma therapy in Ontario

Among the asthma patients newly initiating ICS and LABA therapy between 2008 and 2013, the majority received combination therapy (90%) compared to treatment with concurrent single-agent ICS and LABA products (“dual therapy”). Among the youth (aged 12-17) asthma patients initiating ICS and LABA therapy who received combination therapy, and 20-30% were still on therapy after 1 year of initiation. Adults treated with combination ICS+LABA products differed from those treated with dual therapy, in regards to urban residence, LTC residency, COPD diagnosis, concomitant asthma therapy use and use of other asthma therapy prior to initiation of ICS+LABA. Notably, more dual therapy users had a COPD diagnosis compared to combination therapy users among both young adults (60-70% and 40-50%, respectively) and older adults (80-90% and 60-70%, respectively). Prior use of asthma therapy was generally higher among dual therapy users compared to combination therapy users for all asthma agents. Among younger adults, the proportion of users still on therapy after 1 year was higher among those on combination therapy compared to dual therapy (40-50% and 30-40%, respectively). This was also observed among older adults, with a higher proportion of users still on therapy after 1 year among those on combination therapy (40-50%) compared to dual therapy (40-50%).

Among the youth, younger adult and older adult asthma patients newly initiating ICS+LABA combination therapy between 2008 and 2013, the majority started on an Advair product (55-60%, 60-64% and 60-64%, respectively) compared to a Symbicort product. Zenhale use was not captured during our study period. New users of Advair were more likely to receive multiple prescriptions, receive prior asthma therapies, and be dispensed triple therapy and concomitant asthma therapies compared to new Symbicort users. More Advair users had a COPD diagnosis compared to Symbicort users among young adults (45-49% and 35-39%, respectively) and older adults (70-74% and 55-59%, respectively). Among youth with asthma, the proportion of ICS+LABA users still on therapy after 1 year was lower among those using Advair compared to those using Symbicort (20-24% and 25-29%, respectively). However, there were more Advair users still on therapy after 1 year compared to Symbicort users among younger adults (40-44% and 35-39%, respectively) and older adults (45-49% and 40-44%, respectively).

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Introduction

Inhaled corticosteroids and long-acting beta-agonist (ICS+LABA) combination products are drugs used to manage respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD). Four combination products are available in Canada: Advair (fluticasone and salmeterol), Symbicort (formoterol and budesonide), Zenhale (formoterol and mometasone), and Breo Ellipta (fluticasone and vilanterol). Breo Ellipta is the newest of these products (available November 2013); it is indicated for COPD only, and is not yet on the Ontario public drug formulary. The remaining three products (Advair, Symbicort, and Zenhale) are indicated for the treatment of asthma and/or COPD. In Ontario, all three products are available through the Ontario Drug Benefit (ODB) program with Limited Use criteria for asthma only.

The objectives of this report are to describe national and provincial trends in the use of ICS+LABA combination products and to identify patterns of therapy among patients with asthma who have provincial drug coverage. Specifically, this report aims to:

1. Present national utilization trends of ICS+LABA combination products and asthma drug therapies in Canada, including cross-provincial comparisons of population-adjusted rates of use
2. Examine trends in use of ICS+LABA combination products and asthma drug therapies dispensed through the Ontario Drug Benefit program
3. Describe characteristics of patients with asthma treated with provincially-funded ICS+LABA combination products in Ontario
4. Outline adherence to combination therapy for treatment of asthma in Ontario

Data Sources

IMS Geographic Prescription Monitor (GPM¹²)

IMS Geographic Prescription Monitor (GPM¹²) is a premium source of sales intelligence on retail prescription activity in Canada. Data is obtained from a representative sample of 65% of all Canadian pharmacies and is projected monthly by province or customized geography. Projections incorporate the number of pharmacies in a given area, the distance between IMS-captured and uncaptured pharmacies, and the size of the pharmacies. Projections are representative of provincial and national sales volumes. Data available through IMS Geographic Prescription Monitor (GPM¹²) includes prescription volumes and units (e.g. tablets, patches) dispensed, and are stratified by payer type (e.g. public drug plan, private drug plan, cash, Non-Insured Health Benefits). Data from IMS Geographic Prescription Monitor (GPM¹²) is available from the fourth quarter of 2009 to the last quarter of 2013.

Canadian Institute for Health Information NPDUIS

The National Prescription Drug Utilization Information System (NPDUIS) was developed by the Canadian Institute for Health Information (CIHI) to provide pan-Canadian information on public drug programs.

NPDUIS data can be used to obtain estimates of populations eligible for provincial drug coverage in Alberta, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, and Prince Edward Island. Data is available from NPDUIS from 2000 to 2012.

Ontario Drug Benefit Database

The Ontario Drug Benefit (ODB) database contains individual-level claims data for all prescription drugs dispensed to Ontario residents eligible for public drug funding. Eligibility criteria include unemployment, disability, high prescription drug costs relative to net household income, receipt of home care services, residence in a long-term care facility, and age ≥ 65 years. This database is of high quality, with an error rate of $<1\%$ and can be linked to other health administrative databases to obtain patient demographic information.¹ We analyzed data from the ODB between January 2000 and March 2013.

Ontario Chronic Obstructive Pulmonary Disease Database

The Ontario Chronic Obstructive Pulmonary Disease (COPD) database contains prevalence data on all Ontario COPD patients identified since fiscal year 1991/92. The database was created using hospital discharge abstracts from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), same-day surgery records from the National Ambulatory Care Reporting System (NACRS), physician service claims from the Ontario Health Insurance Plan (OHIP) claims database, and demographic information on persons eligible for health care coverage in Ontario from the Registered Persons Database (RPDB). The case definition for COPD uses 1 or more ambulatory care claims and/or 1 or more hospitalizations for COPD to ascertain prevalence, and yielded a sensitivity of 85% (95% confidence interval [CI] 77-91%) and specificity of 78.4% (95% CI 73.6-82.7%) when compared to a clinical reference standard.²

Ontario Asthma Database

The Ontario Asthma database contains prevalence data on all Ontario asthma patients identified since fiscal year 1993/94. The database was created using hospital discharge abstracts from CIHI-DAD, same-day surgery records from NACRS, physician service claims from OHIP, and demographic information from RPDB. The case definition for asthma uses 1 or more hospitalizations and/or 2 or more ambulatory care visits for asthma within 2 years to ascertain prevalence, and yielded a sensitivity of 83.8% (95% CI 77.1-89.1%) and specificity of 76.5% (95% CI 71.8-80.8%) in a chart abstraction validation study.³

Methods

All analyses described below were approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Ontario.

National Trends in Utilization of ICS+LABA Combination Products

We used data from IMS Geographic Prescription Monitor (GPM¹²) to examine overall trends in the prescribing volumes of therapies use to treat asthma, including inhaled anti-inflammatory agents, bronchodilator agents, and combination products, at both national and provincial levels. We examined

the number of prescriptions dispensed for inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), ICS+LABA combination products, short-acting beta-agonists (SABA), long-acting anti-muscarinic agents (LAMA), short-acting anti-muscarinic agents (SAMA), leukotriene receptor antagonists (LTRA), Anti-IgE agents and theophylline agents dispensed between October 2009 and December 2013. Note that in these analyses, we were unable to restrict prescription volumes specifically to those patients with asthma, and therefore these represent all use of these medications for any indication. Analyses were stratified by payer (provincially-funded vs. non-provincially-funded). Provincially-funded prescriptions were those paid for through public drug programs; non-provincially-funded prescriptions were those paid for through private insurance plans, cash payments, or Non-Insured Health Benefits (NIHB). All cross-provincial analyses compared population-adjusted rates.

Population Adjustment – Overall Utilization

Provincial population estimates were obtained from Statistics Canada for each year from 2009 to 2013 and used to adjust the overall utilization rates of ICS+LABA combination products across the different provinces.

Population Adjustment – Stratified by Payer

For measures examining provincially-funded utilization of ICS+LABA combination products, we used the number of individuals eligible for provincial drug coverage in each year from 2009 to 2013 to standardize utilization rates. In the case of provinces where we had individual-level data available through NPDUIS and ODB (i.e. Alberta, Manitoba, Saskatchewan, Ontario, New Brunswick, Nova Scotia and Prince Edward Island), we defined the number of eligible beneficiaries in each year as any individual who had at least one publically funded drug claim over the time period. In the case of British Columbia, Quebec, and Newfoundland and Labrador, we obtained estimates of eligible populations from the annual reports of each public drug program. For all provinces, eligible population counts for the most recent years were estimated using linear extrapolation where data was not available.

Because all individuals (both those eligible for public drug programs and non-beneficiaries) might pay for ICS+LABA combination products out of pocket, measures of non-provincially-funded utilization were adjusted using overall provincial population estimates from Statistics Canada.

Trends in Provincially-Funded ICS+LABA Combination Products

We used claims data from ODB to perform additional analyses of utilization of ICS+LABA combination products among patients with asthma in Ontario. These analyses included estimating the market share and costs of inhaled anti-inflammatory agents and bronchodilators (including ICS, LABA, ICS+LABA combination products, LAMA, SABA, SAMA and LTRA) as well as the number of users of publically-funded combination products. We also looked at demographic characteristics of patients dispensed ICS+LABA combination products for the treatment of asthma.

Adherence among New Users of ICS+LABA Combination or Dual Therapy

We established a cohort of new users of ICS+LABA combination products between April 1, 2008 and March 31, 2012 to examine the duration of combination therapy in Ontario. We defined ICS+LABA combination therapy as either use of an ICS+LABA combination product, or as concurrent use of ICS and LABA single agents. We followed each individual forward from the time of their first prescription (if using a combination product) or from the time of the first concurrent prescription (if using ICS and LABA single agents) until they discontinued combination therapy, died, had 2 years of follow-up, or reached the end of the study period (March 31, 2013). Discontinuation was defined on the basis of refills for combination products (or ICS and LABA single agents) within 180 days of the previous prescription, which is consistent with previously published studies.^{4, 5} A sensitivity analysis was performed defining discontinuation on the basis of refills for combination products (or ICS and LABA single agents) within 1.5 times the day supply of the previous prescription.

Indications for ICS+LABA combination products

There are currently four ICS+LABA combination products marketed in Canada.

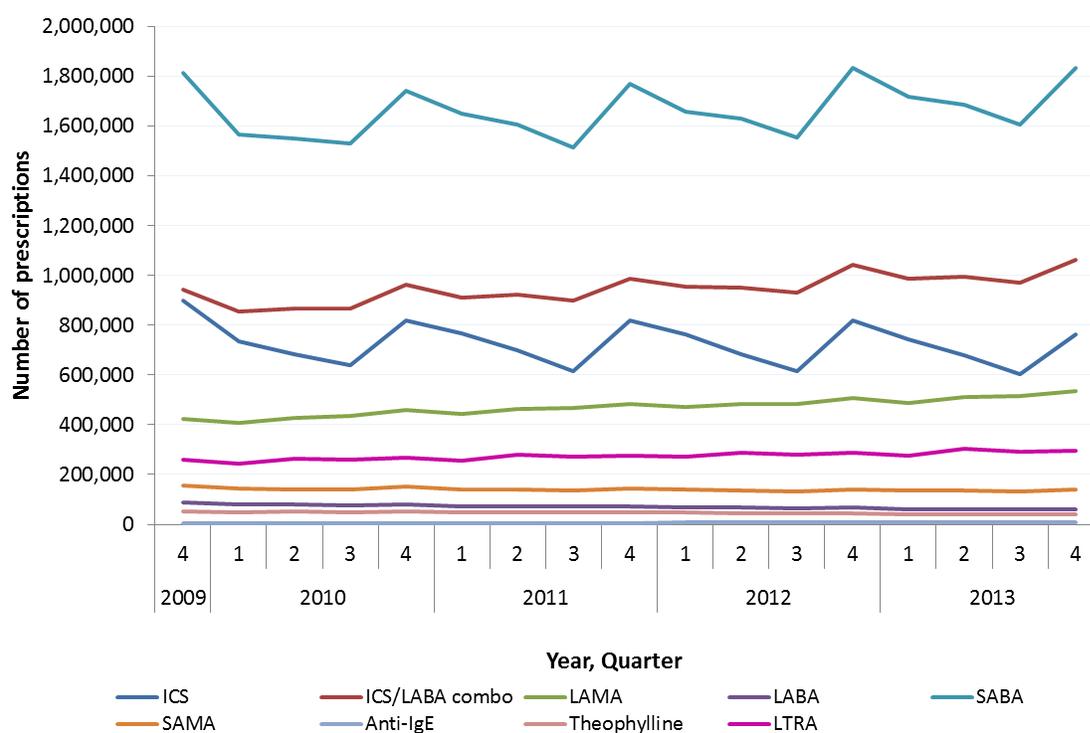
1. **Advair** (fluticasone and salmeterol) is available in both Diskus (dry powder inhaler, DPI) and metered dose inhaler (MDI) formulations. Advair Diskus was listed on the Canadian market in September 1999, and is indicated for both asthma and COPD. The MDI formulation was added to the market in December 2001, and is only indicated for asthma.
2. **Symbicort** (formoterol and budesonide) was added to the market in February 2002. Symbicort is available in a DPI formulation and is indicated for both asthma and COPD.
3. **Zenhale** (formoterol and mometasone) is available as a metered dose inhaler and was added to the market in March 2011. Zenhale is only indicated for the treatment of asthma.
4. Breo **Ellipta** (fluticasone and vilanterol) is available in a DPI formulation. It was introduced onto the Canadian market in November 2013 and is only indicated for COPD.

Advair, Symbicort and Zenhale are listed on the Ontario public drug formulary for the treatment of asthma. Since Breo Ellipta is not indicated for the treatment of asthma and is not listed on the Ontario public drug formulary it is not included in any of the analyses in this report.

Exhibits and Findings

National Trends in Utilization of Inhaled Anti-Inflammatory and Bronchodilator Therapies

Exhibit 1: Total number of prescriptions for inhaled anti-inflammatory and bronchodilator agents dispensed in Canada, by quarter

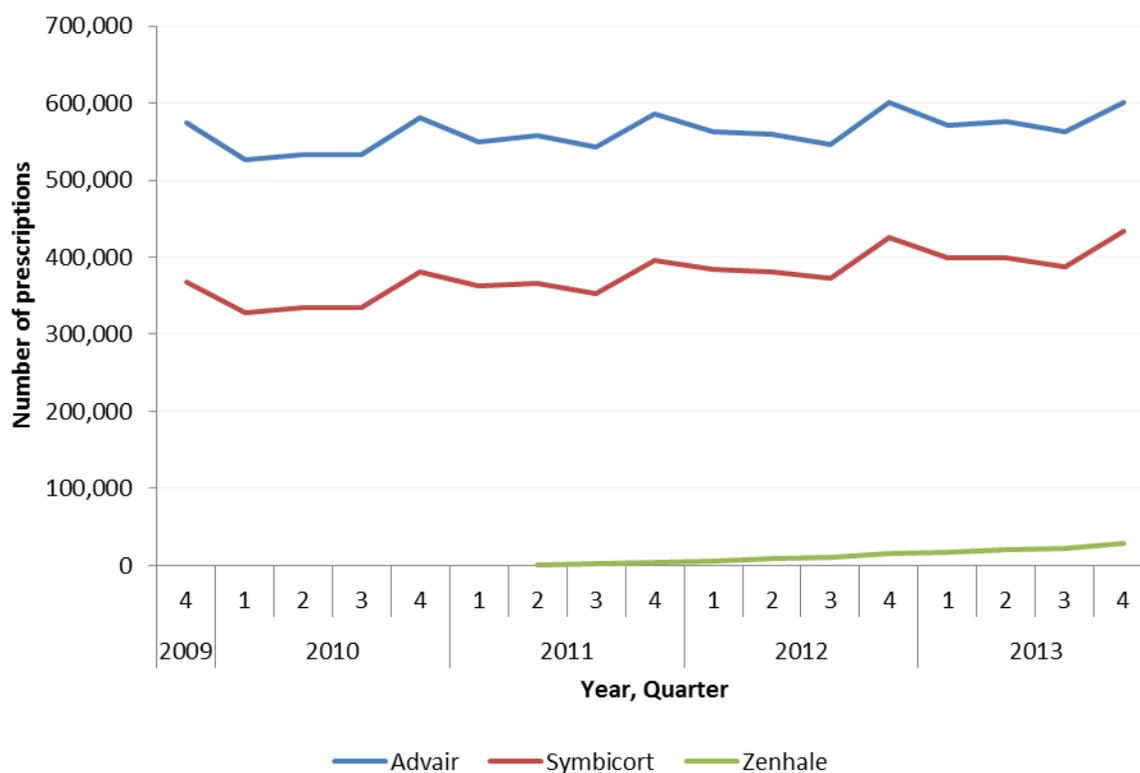


ICS+LABA combination products are the second most commonly dispensed anti-inflammatory/bronchodilator agents in Canada.

Summary of Findings for Exhibit 1

1. The prescription market share in the fourth quarter (Q4) of 2013 was:
 - a. Short-acting beta-agonists (SABA) products: 38.7%; 1.8 million prescriptions
 - b. Inhaled corticosteroid/long-acting beta-agonist (ICS+LABA) combination products: 22.4%; 1.1 million prescriptions
 - c. Inhaled corticosteroids (ICS): 16.1%; 761,746 prescriptions
 - d. Long-acting anti-muscarinic agents (LAMA): 11.3%; 536,148 prescriptions
 - e. Short-acting anti-muscarinic agents (SAMA): 3.0%; 140,942 prescriptions
 - f. Long-acting beta-agonists (LABA): 1.3%; 60,283 prescriptions
 - g. Leukotriene receptor antagonists (LTRA): 6.2%; 293,909 prescriptions
 - h. Anti-IgE agents: 0.2%; 8,972 prescriptions
 - i. Theophylline pills: 0.8%; 41,026 prescriptions

Exhibit 2: Total utilization of ICS+LABA combination products in Canada, by product and quarter



Utilization of ICS+LABA combination products has increased slightly over the past 4 years. Advair remains the most commonly dispensed combination product in Canada.

Summary of Findings for Exhibit 2

1. The use of ICS+LABA combination products has increased approximately 13% over the past 4 years from 942,397 prescriptions (Q4 2009) to 1.1 million prescriptions (Q4 2013).
2. Among all ICS+LABA prescriptions dispensed in Q4 2013 (1.1 million), over half (57%; 600,340 prescriptions) were for Advair, followed by Symbicort (40%; 433,892 prescriptions) and Zenhale (3%; 29,201 prescriptions).
3. Since its introduction to the Canadian market in early 2011, the number of prescriptions for Zenhale has increased from 939 prescriptions (Q3 2011) to 29,201 prescriptions (Q4 2013).
4. In the last quarter of 2013, a total of \$83.5 million was spent on Advair, \$42.5 million was spent on Symbicort, and \$3.2 million was spent on Zenhale, nationally (data not shown). Although Advair use is almost 1.5-fold greater than Symbicort use, cost is almost 2-fold greater. This may be due to Advair having a higher cost per unit compared to Symbicort (\$139.2 and \$98.1 per unit in Q4 2013, respectively) (data not shown).
5. Trends in utilization and costs of ICS+LABA combination products in Ontario are similar to those across Canada. Advair had the highest utilization and costs, followed by Symbicort and Zenhale. A total of \$52.5 million was spent on combination products in Ontario in the last quarter of 2013 (40.6% of total national expenditures) (data not shown).

Population-adjusted rates of ICS+LABA utilization, by funding type

Methodological Note:

Non-provincially funded use represents use outside of provincial drug plans. This includes prescriptions paid by:

- Private drug insurance
- Cash
- Non-Insured Health Benefits

Public plan listings for ICS+LABA combination products across the provinces are as follows:

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

Public drug plan eligibility also differs by province which may impact the average age of beneficiaries. More detailed information on public plan listings is provided in Appendix C.

Exhibit 3: Population-adjusted utilization of provincially funded ICS+LABA combination products in Canada, by province

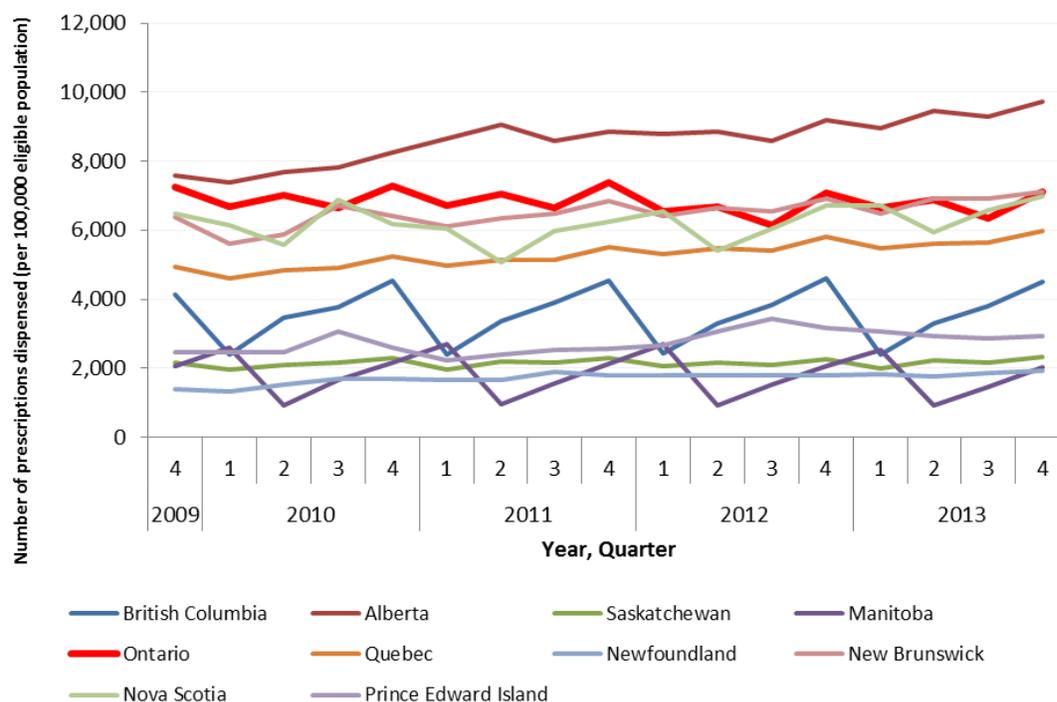
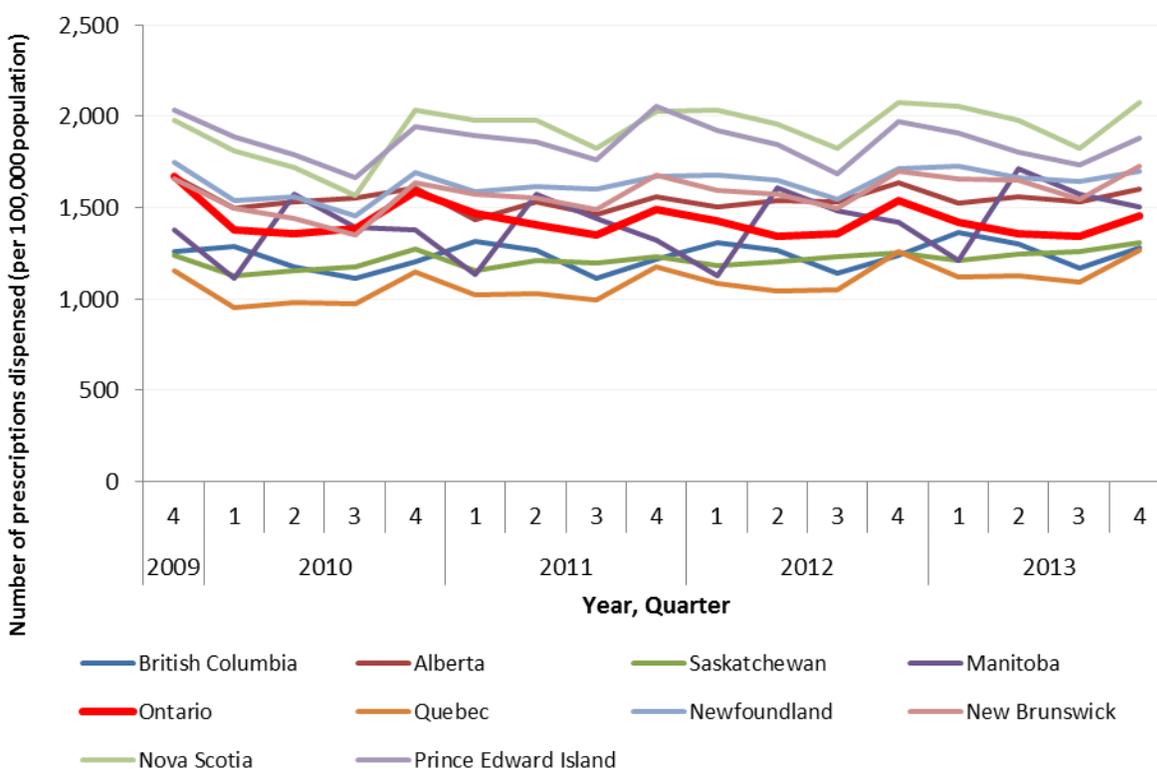


Exhibit 4: Population-adjusted utilization of non-provincially funded ICS+LABA combination products in Canada, by province



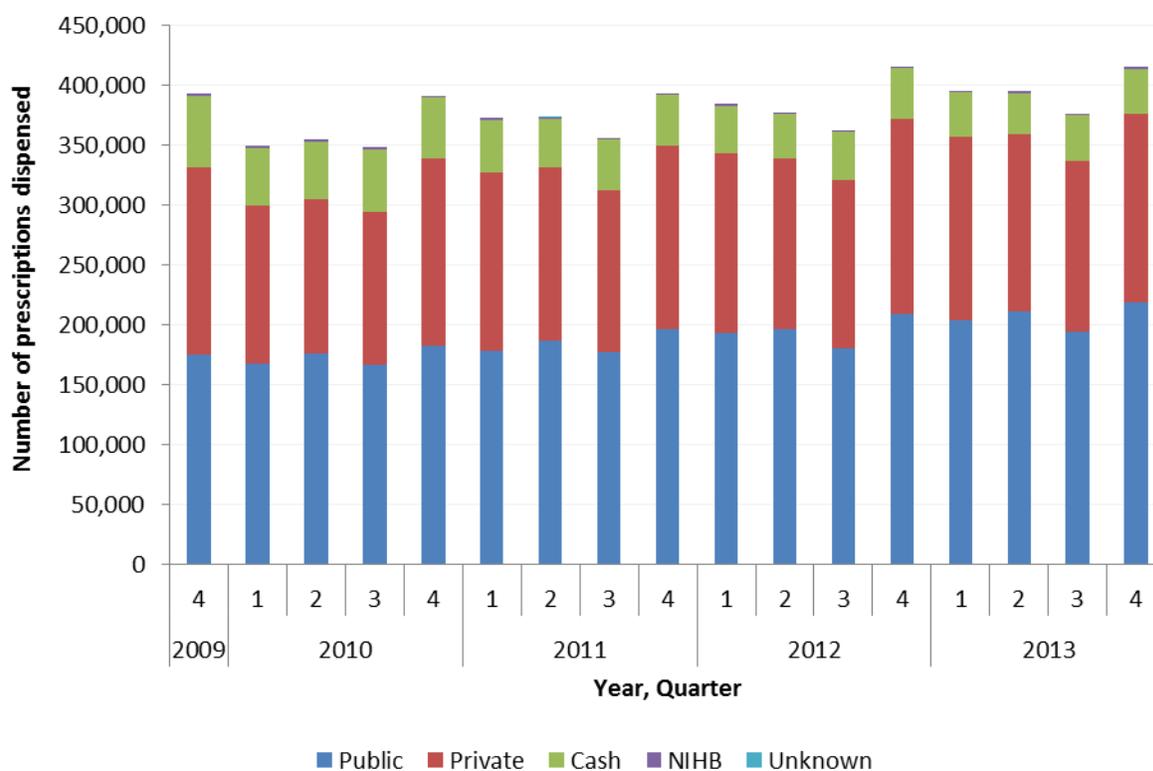
Ontario has the second highest utilization of provincially funded ICS+LABA combination products in Canada. Non-provincially funded ICS+LABA use in Ontario was on par with the national average.

Summary of Findings for Exhibit 3 & Exhibit 4

1. There was wide variation in the number of provincially funded ICS+LABA prescriptions dispensed between provinces (range in Q4 2013: 1,925 [Newfoundland] to 9,716 [Alberta] prescriptions per 100,000 eligible population). The high rate of use of ICS+LABA combination products in Alberta may reflect unrestricted access to these medications through the public drug program (i.e. Advair and Symbicort are listed as general benefit on the provincial formulary). However, Manitoba had considerably lower utilization of ICS+LABA combination despite their general benefit listing.
2. There was much less cross-provincial variation in prescribing trends amongst non-provincially funded products (range in Q4 2013: 1,270 [Quebec] to 2,078 [Nova Scotia] prescriptions per 100,000 eligible population).
3. In Q4 2013, Ontario had the second highest rate of provincially funded ICS+LABA use (7,127 prescriptions per 100,000 eligible population compared to the national average of 5,063 prescriptions per 100,000 eligible population). This may be due to the passive restrictive listing for Advair and Symbicort use in Asthma.
4. Non-provincially funded ICS+LABA use in Ontario was on par with the national average (1,453 prescriptions per 100,000 eligible population and 1,580 prescriptions per 100,000 eligible population, respectively).

Trends in Provincially-Funded ICS+LABA Combination Products in Ontario

Exhibit 5: Total utilization of ICS+LABA combination products in Ontario, by coverage



53% of ICS+LABA combination products were paid for by the Ontario Public Drug Program in the last quarter of 2013. More than 85% of ICS+LABA combination products have been paid for by private or provincially-funded drug coverage in Ontario since Q4 2009.

Summary of Findings for Exhibit 5

1. The number of prescriptions dispensed for ICS+LABA combination products in Ontario has increased 5.7%, from 392,377 prescriptions at the end of 2009 to 414,629 prescriptions at the end of 2013.
2. The majority of prescriptions (52.6%) for ICS+LABA combination products dispensed in Ontario are paid for by provincial drug coverage. This has increased 24.6% from 174,869 prescriptions in Q4 2009 to 217,935 in Q4 2013.
3. A small proportion of ICS+LABA combination products are paid for by cash or Non-Insured Health Benefits (NIHB), which has decreased from 15.5% in Q4 2009 to 9.3% in Q4 2013.
4. By Q4 2013, the distribution of payers for ICS+LABA combination products dispensed in Ontario was 52.6% public, 38.1% private, 9.0% cash, and 0.3% NIHB.

Exhibit 6: Total utilization of asthma therapy products among public drug plan beneficiaries with asthma in Ontario, age 12-17, by product and fiscal year

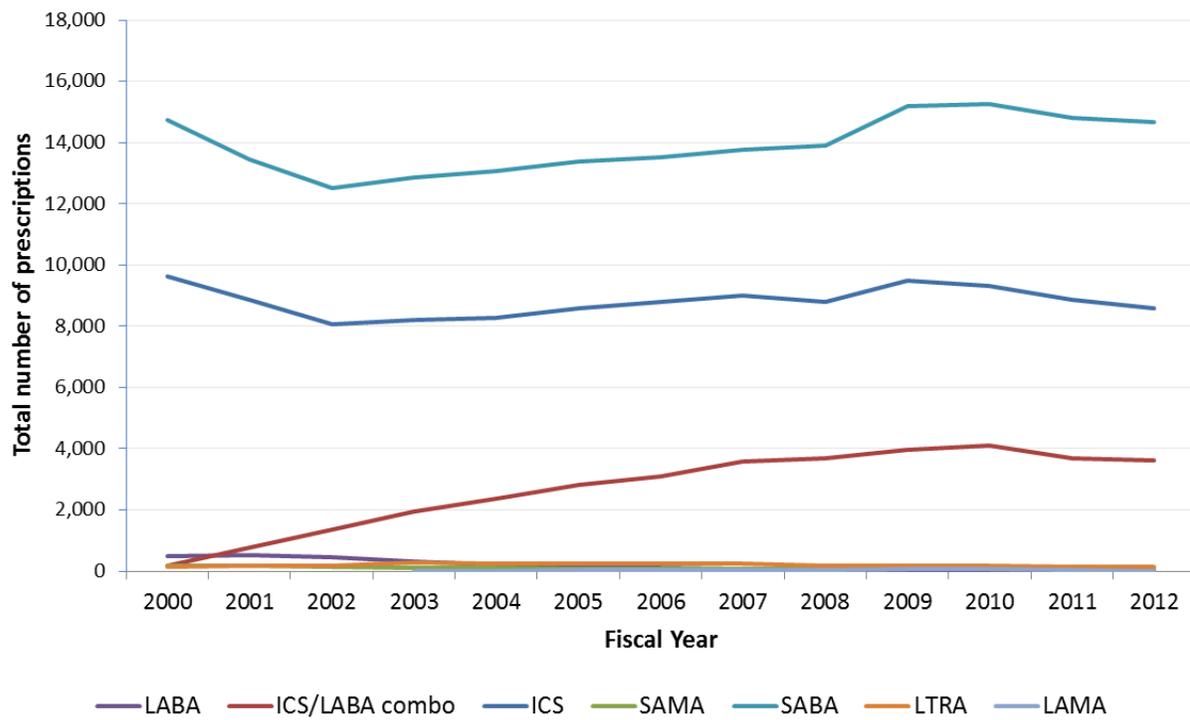


Exhibit 7: Total utilization of asthma therapy products among public drug plan beneficiaries with asthma in Ontario, age 18-64, by product and fiscal year

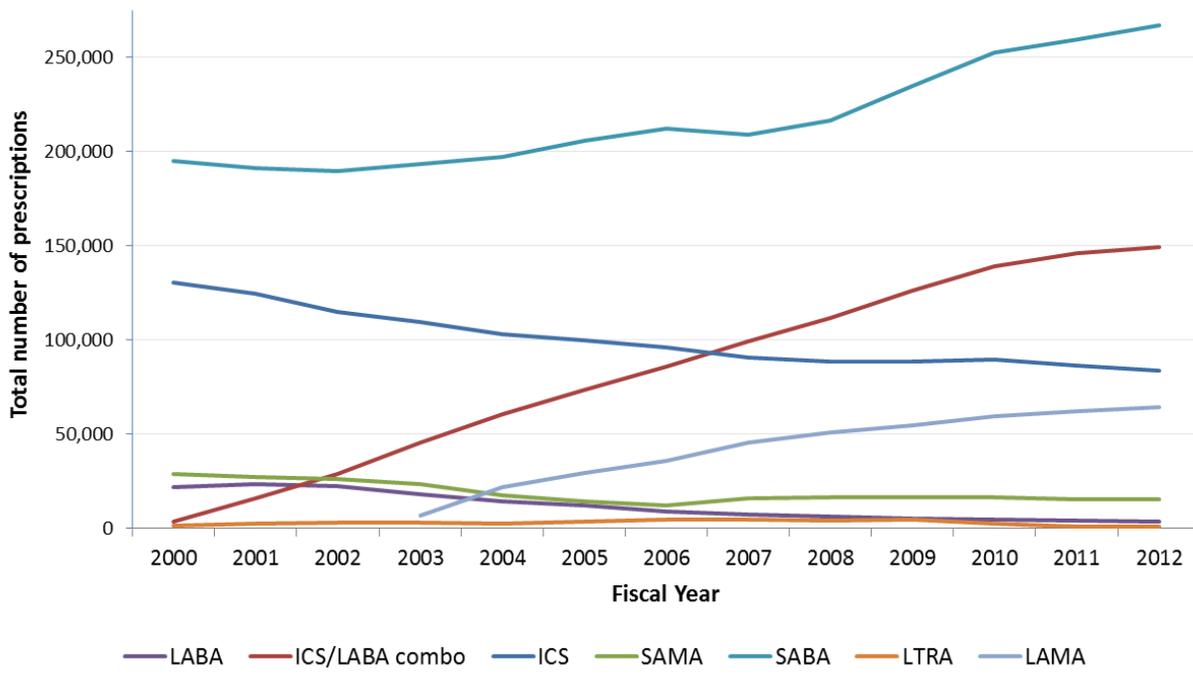
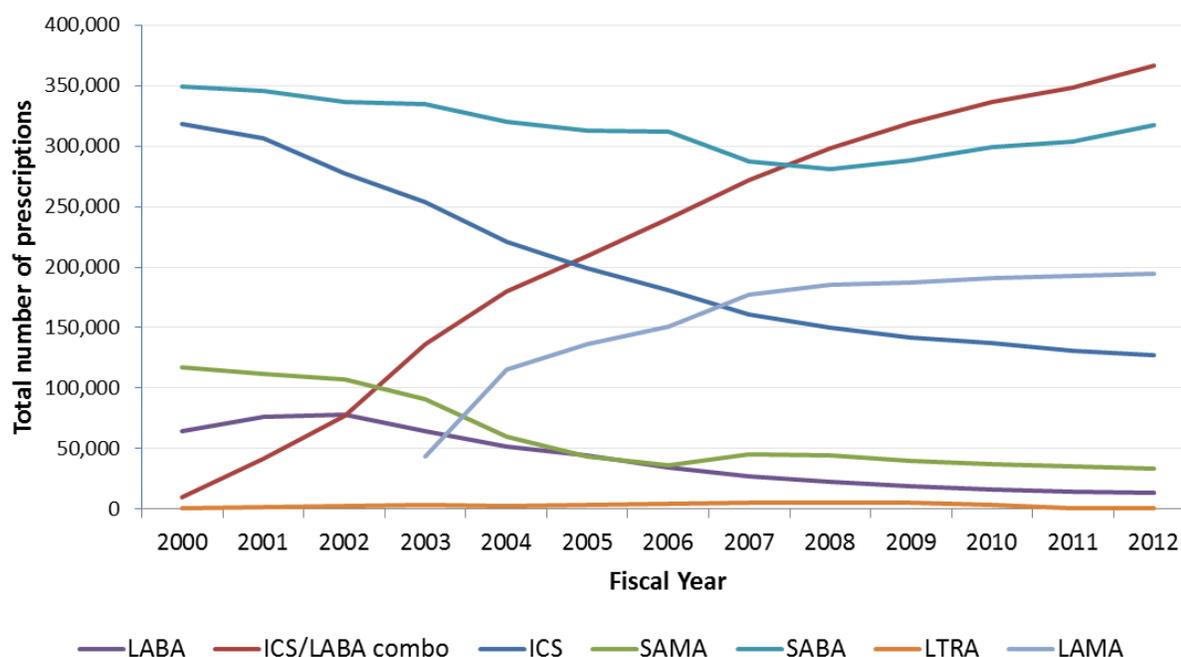


Exhibit 8: Total utilization of asthma therapy products among public drug plan beneficiaries with asthma in Ontario, age 65+, by product and fiscal year

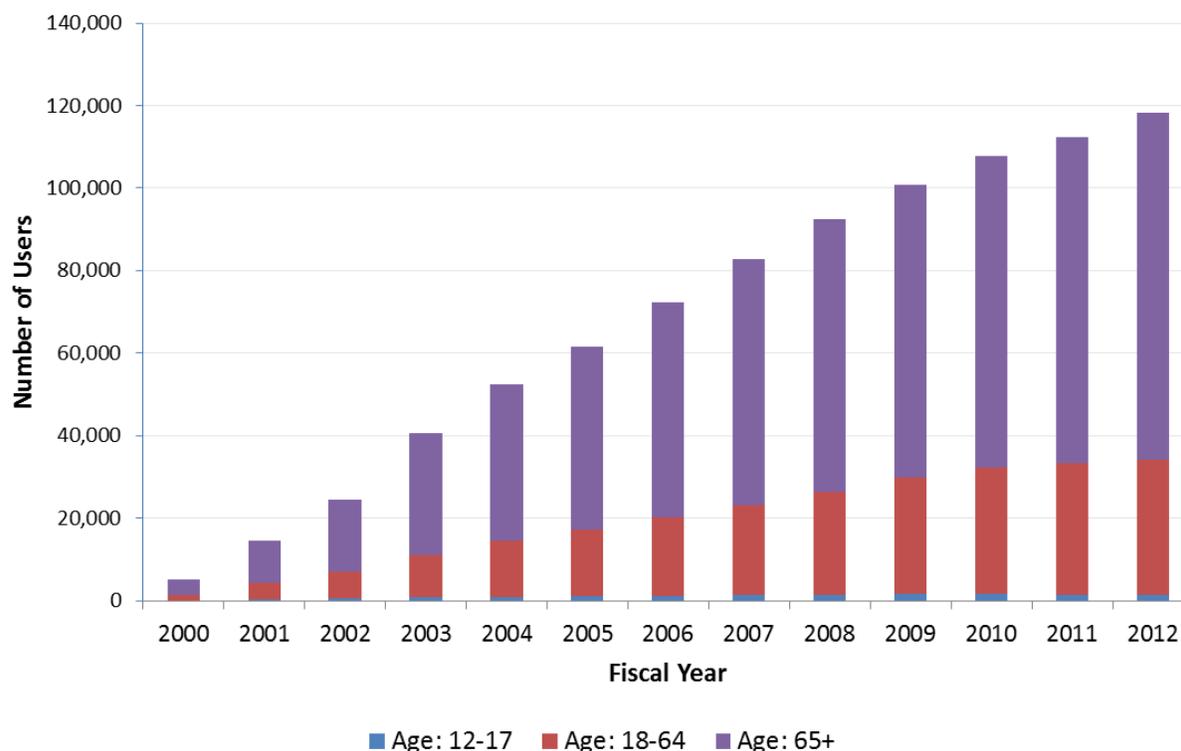


The use of ICS+LABA combination products among individuals with asthma has been increasing markedly over time. ICS+LABA combination products have been the most commonly dispensed product among individuals 65 years of age and older since 2008.

Summary of Findings for Exhibit 6, Exhibit 7 and Exhibit 8

1. The number of prescriptions dispensed for ICS+LABA combination products among patients with asthma has increased 37-fold, from 14,133 prescriptions in 2000 to 519,287 prescriptions in 2012. This increase was largely driven by the 36-fold increase in the number of prescriptions dispensed to older adults (aged 65 and older) over the study period [10,258 prescriptions (2000) to 366,307 prescriptions (2012)].
2. SABAs remained the most commonly dispensed respiratory product among individuals with asthma aged 12-17 (youth) and 18-64 years (young adults) [55% (14,681 out of 27,112 prescriptions) and 50% (2.8 million out of 5.8 million prescriptions) in 2012, respectively].
3. Among youth, ICS was the second most commonly dispensed therapy followed by ICS+LABA therapy in 2012 (8,584 and 3,623 prescriptions, respectively).
4. Among young adults, ICS/LABA was the second most commonly dispensed therapy, followed by the declining use of ICS and increasing use of LAMA therapy (149,357, 83,666 and 64,345 prescriptions in 2012).
5. Among older adults, ICS/LABA therapy was the most commonly dispensed therapy by 2012.
6. Over the study period, there was a decline in the number of single-agent ICS and LABA products among all age groups.

Exhibit 9: Number of users of provincially-funded ICS+LABA combination products with asthma in Ontario, by age and fiscal year

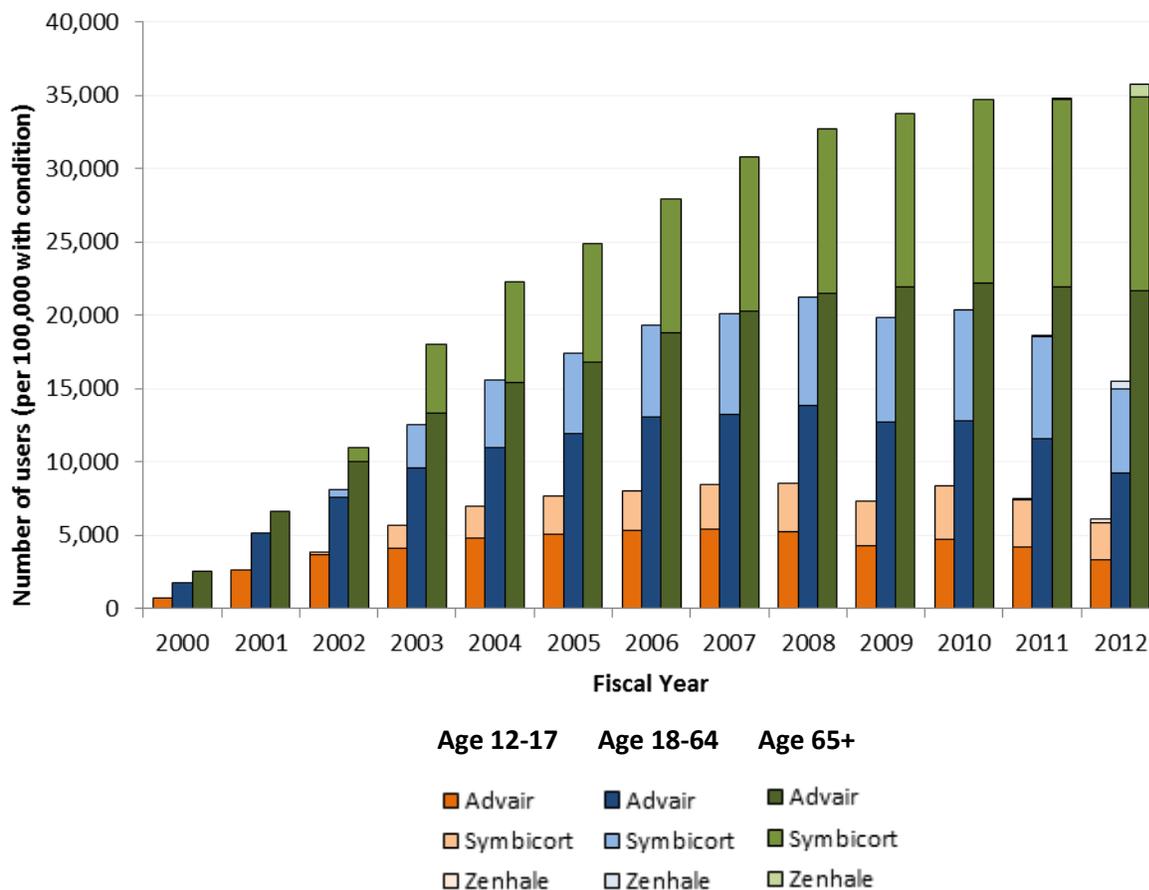


Among individuals with asthma the majority (71%) of ICS+LABA combination products are used by individuals aged 65 years and older

Summary of Findings for Exhibit 9

1. Use of ICS+LABA combination products among individuals with asthma has increased nearly 23-fold from 5,069 users in 2000 to 118,178 users in 2012.
2. Younger adults (aged 18-64) had a slightly higher increase in the number of ICS+LABA users than older adults (aged 65 and older) between 2000 and 2012 (24-fold vs. 23-fold). A 16-fold increase was noted in youth (aged 12-17) during the study period.
3. By fiscal year 2012, 84,143 (71.2%) older adults, 32,686 (27.7%) younger adults and 1,349 (1.1%) youth with asthma were dispensed an ICS+LABA combination product.

Exhibit 10: Utilization rates of provincially-funded ICS+LABA combination products among patients with asthma in Ontario, by age and product



Rates of Advair, Symbicort, and Zenhale use have increased over time among all age groups. Advair had the highest utilization rates over time across all age groups.

Summary of Findings for Exhibit 10

1. Utilization rates of ICS+LABA combination products have increased substantially in Ontario with the largest increase among older adults (aged 65 and older) [58-fold, from 99 users per 100,000 patients with asthma (Q3 2000) to 5,729 users per 100,000 patients with asthma (Q1 2013)].
2. Similarly, the rate of use has increased 23-fold in youth (aged 12-17) [from 55 per 100,000 patients (Q3 2000) to 1,241 per 100,000 patients (Q1 2013)], and 34-fold in younger adults (aged 18-64) [from 101 users per 100,000 patients (2000) to 3,426 per 100,000 patients (2013)].
3. A decline in the rate of use was observed among youth and young adults with asthma between 2011 and 2013. Among youth, the rate of use declined 36%, from 1,929 users per 100,000 patients (Q1 2011) to 1,241 users per 100,000 patients (Q1 2013). Similarly, the rate of use among young adults declined 22%, from 4,399 users per 100,000 patients (Q1 2011) to 3,426 users per 100,000 patients (Q1 2013).
4. Rates of Advair use have increased among patients with asthma between fiscal years 2000 and 2012 in all age groups, from 727 to 3,310 users per 100,000 patients for youth, 1,754 to 9,257 users per 100,000 patients for younger adults, and 2,542 to 21,669 users per 100,000 patients for older adults.
5. Symbicort was added to the Ontario public drug formulary in February 2002. Since then, rates of Symbicort use have increased more than 10-fold among beneficiaries with asthma between fiscal years 2002 and 2012 in all age groups, from 209 to 2,529 users per 100,000 patients for youth, 499 to 5,758 users per 100,000 patients for younger adults, and 918 to 13,217 users per 100,000 for older adults.
6. Zenhale was added to the public drug formulary in February 2012. In fiscal year 2012, there were 265, 481, and 888 Zenhale users per 100,000 patients in the youth, younger adult and older adult age groups, respectively.
7. The proportion of asthma patients using Advair and Symbicort has changed over time, reflecting the additions of Symbicort and Zenhale to the public drug formulary. By fiscal year 2012, Advair was still the most commonly used ICS+LABA product followed by Symbicort among youth (54.2% and 41.4%, respectively), younger adults (59.7% and 37.2%, respectively) and older adults (60.6% and 36.9%, respectively) with asthma. Zenhale was used by less than 5% of youth, younger adults and older adults with asthma who used ICS+LABA combination products.

Exhibit 11: Overall drug cost and average drug cost per user of ICS+LABA combination products among patients with asthma in Ontario, by age and product in fiscal year 2012

AGE GROUP	BY PRODUCT					
	ADVAIR		SYMBICORT		ZENHALE	
	OVERALL COST	AVERAGE COST PER USER	OVERALL COST	AVERAGE COST PER USER	OVERALL COST	AVERAGE COST PER USER
12-17	\$271,607.91	\$ 362.14	\$136,850.03	\$238.83	\$10,600.92	\$176.68
18-64	\$14,209,436.18	\$697.88	\$5,479,088.58	\$432.62	\$316,341.01	\$299.28
65+	\$41,981,720.42	\$791.27	\$15,968,954.99	\$493.45	\$782,215.88	\$359.64

In fiscal year 2012, the average drug cost per user was highest for Advair and lowest for Zenhale in Ontario. Average costs were highest for users aged 65 and older.

Summary of Findings for Exhibit 11

1. In fiscal year 2012, \$79.1 million was spent on ICS/LABA combination products dispensed to Ontario public drug plan beneficiaries with asthma. Costs for older adults (aged 65 and older) accounted for 74.2% (\$58.7 million) of the total costs, while younger adults (aged 18-64) accounted for 25.3% (\$20.0 million) of the total costs and youths (aged 12-17) accounted for 0.5% (\$419,059) of the total costs.
2. The total cost of Advair in fiscal year 2012 was \$56.4 million (71% of total ICS/LABA costs). Older adult beneficiary costs accounted for 74.4% (\$41.9 million) of the total costs of Advair use, and younger adult beneficiary costs accounted for 25.2% (\$14.2 million) of the total costs of Advair use. Youth beneficiary costs accounted for 0.5% (\$271,608) of the total costs of Advair use.
3. The total cost of Symbicort use in fiscal year 2012 was \$21.5 million (27% of total ICS/LABA costs). Older adult beneficiary costs accounted for 74.0% (\$16.0) of the total costs of Symbicort use, and younger adult beneficiary costs accounted for 25.38% (\$5.5 million) of the total costs of Symbicort use. Youth beneficiary costs contributed to 0.63% (\$136,850) of the total costs of Symbicort use.
4. Zenhale use accounted for 1% of total ICS/LABA costs (\$1.1 million) in fiscal year 2012. Older adult beneficiary costs accounted for the majority (70.5%) of the total costs of Zenhale use.
5. Among individuals with asthma, the average cost per user for ICS/LABA products was \$643.2. Beneficiaries using Advair had the highest average costs per user (\$761.29), followed by Symbicort users (\$473.35) and Zenhale users (\$336.93).
6. Older adult beneficiaries had the highest ICS/LABA average costs per user (\$670.5), followed by younger adult beneficiaries (\$587.0) and youth beneficiaries (\$303.0).

Characteristics of provincially-funded ICS+LABA combination product users with asthma in Ontario

Exhibit 12: Baseline characteristics of asthma patients aged 12-17, treated with provincially-funded ICS+LABA combination products in Ontario, by product, fiscal year 2012/13

	Overall N (%)	Advair Diskus N (%)	Advair HFA ¹ N (%)	Symbicort N (%)	Zenhale ² N (%)
Prescription level measures					
Number of puffs dispensed, per user Median (IQR)	240.0 (120.0-480.0)	120.0 (60.0-300.0)	240.0 (120.0-480.0)	240.0 (120.0-480.0)	120.0 (120.0-240.0)
Number of puffers dispensed, per user Median (IQR)	2.0 (1.0-4.0)	2.0 (1.0-5.0)	2.0 (1.0-5.0)	2.0 (1.0-4.0)	1.0 (1.0-2.0)
Cost of ICS+LABA prescriptions, per user (Mean, SD)³	344.7 (346.2)	394.0 (385.7)	427.7 (408.5)	267.7 (250.7)	192.4 (155.7)
ODB plan					
<i>ODSP</i>	559 (55.5%)	147 (56.5%)	167 (56.4%)	225 (54.2%)	20 (55.6%)
<i>Ontario Works</i>	313 (31.1%)	79 (30.4%)	85 (28.7%)	139 (33.5%)	10 (27.8%)
<i>Trillium</i>	134 (13.3%)	34 (13.1%)	43 (14.5%)	51 (12.3%)	6 (16.7%)
<i>Home Care</i>	≤5	0 (0.0%)	≤5	0 (0.0%)	0 (0.0%)
Asthma maintenance therapy (past year)					
<i>ICS</i>	272 (27.0%)	64 (24.6%)	77 (26.0%)	114 (27.5%)	17 (47.2%)
<i>LABA</i>	≤5	≤5	0 (0.0%)	0 (0.0%)	0 (0.0%)
<i>LAMA</i>	≤5	≤5	≤5	0 (0.0%)	0 (0.0%)
<i>LTRA</i>	13 (1.3%)	≤5	≤5	6 (1.4%)	0 (0.0%)
<i>SAMA</i>	≤5	0 (0.0%)	≤5	0 (0.0%)	≤5
<i>SABA</i>	707 (70.2%)	187 (71.9%)	225 (76.0%)	267 (64.3%)	28 (77.8%)
<i>OCS</i>	149 (14.8%)	35 (13.5%)	39 (13.2%)	66 (15.9%)	9 (25.0%)
<i>Theophylline</i>	≤5	0 (0.0%)	≤5	0 (0.0%)	0 (0.0%)
Asthma exacerbations (past year)⁴	102 (10.1%)	33 (12.7%)	22 (7.4%)	42 (10.1%)	≤5

	Overall N (%)	Advair Diskus N (%)	Advair HFA ¹ N (%)	Symbicort N (%)	Zenhale ² N (%)
Person level measures					
Number of asthma patients treated	1,007 (100.0%)	260 (100.0%)	296 (100.0%)	415 (100.0%)	36 (100.0%)
Number of new ICS+LABA users	646 (64.2%)	165 (63.5%)	165 (63.5%)	281 (67.7%)	35 (97.2%)
Age (Median, IQR)	15.3 (13.5-16.7)	15.5 (13.8-17.0)	14.8 (13.2-16.5)	15.4 (13.8-16.9)	14.8 (13.2-16.6)
Males	531 (52.7%)	135 (51.9%)	166 (56.1%)	213 (51.3%)	17 (47.2%)
Prescribed Treatment Step⁵					
Step 3	54 (5.4%)	43 (16.5%)	6 (2.0%)	≤5	≤5
Step 4	761 (75.6%)	184 (70.8%)	172 (58.1%)	389 (93.7%)	16 (44.4%)
Step 5	192 (19.1%)	33 (12.7%)	118 (39.9%)	22 (5.3%)	19 (52.8%)
LTC resident	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Urban residence	903 (89.7%)	239 (91.9%)	271 (91.6%)	357 (86.0%)	36 (100.0%)
Socioeconomic status					
Q1 (lowest)	460 (45.7%)	121 (46.5%)	153 (51.7%)	166 (40.0%)	20 (55.6%)
Q2	246 (24.4%)	68 (26.2%)	*	106 (25.5%)	≤5
Q3	148 (14.7%)	*	41 (13.9%)	66 (15.9%)	≤5
Q4	100 (9.9%)	23 (8.8%)	*	51 (12.3%)	≤5
Q5 (highest)	51 (5.1%)	*	13 (4.4%)	24 (5.8%)	≤5

¹ HFA = 1,1,1,2-tetrafluoroethane (propellant)

² Zenhale added to the provincial drug formulary in February 2012

³ Over fiscal year 2012/13

⁴ Defined as hospitalization or ED visits related to asthma

⁵ Based on calculated ICS daily dose (details in Appendix D)

*In accordance with ICES privacy policies, cells ≤5 have been suppressed with. In the case that the number of users was ≤5, all relevant measures have been suppressed as well, in order to avoid residual disclosure of small cells.

Exhibit 13: Baseline characteristics of asthma patients aged 18-65, treated with provincially-funded ICS+LABA combination products in Ontario, by product, fiscal year 2012/13

	Overall N (%)	Advair Diskus N (%)	Advair HFA ¹ N (%)	Symbicort N (%)	Zenhale ² N (%)
Prescription level measures					
Number of puffs dispensed, per user Median (IQR)	360.0 (120.0-720.0)	300.0 (120.0-600.0)	480.0 (240.0-960.0)	480.0 (240.0-960.0)	240.0 (120.0-480.0)
Number of puffers dispensed, per user Median (IQR)	4.0 (2.0-9.0)	5.0 (2.0-10.0)	4.0 (2.0-8.0)	4.0 (2.0-8.0)	2.0 (1.0-4.0)
Cost of ICS+LABA prescriptions, per user Mean (SD)³	641.7 (548.7)	763.3 (595.4)	722.2 (575.3)	481.2 (431.2)	320.8 (323.4)
ODB plan					
<i>Seniors</i>	2,738 (8.4%)	1,035 (8.2%)	504 (7.0%)	1,137 (9.5%)	62 (9.7%)
<i>ODSP</i>	18,989 (58.5%)	7,700 (60.9%)	4,562 (63.1%)	6,406 (53.7%)	321 (50.4%)
<i>Ontario Works</i>	5,496 (16.9%)	1,900 (15.0%)	1,202 (16.6%)	2,244 (18.8%)	150 (23.5%)
<i>LTC</i>	81 (0.3%)	*	*	*	≤5
<i>Homes for Special Care</i>	14 (0.04%)	≤5	≤5	*	0 (0.0%)
<i>Trillium</i>	4,792 (14.8%)	1,855 (14.7%)	838 (11.6%)	2,003 (16.8%)	96 (15.1%)
<i>Home Care</i>	344 (1.1%)	122 (1.0%)	84 (1.2%)	131 (1.1%)	*
Asthma maintenance therapy (past year)					
<i>ICS</i>	5,768 (17.8%)	2,015 (15.9%)	1,522 (21.1%)	1,957 (16.4%)	274 (43.0%)
<i>LABA</i>	238 (0.7%)	87 (0.7%)	52 (0.7%)	85 (0.7%)	14 (2.2%)
<i>LAMA</i>	8,052 (24.8%)	3,878 (30.6%)	1,758 (24.3%)	2,335 (19.6%)	81 (12.7%)
<i>LTRA</i>	34 (0.1%)	9 (0.1%)	12 (0.2%)	12 (0.1%)	≤5
<i>SAMA</i>	1,862 (5.7%)	834 (6.6%)	526 (7.3%)	472 (4.0%)	30 (4.7%)
<i>SABA</i>	23,285 (71.7%)	9,598 (75.9%)	5,625 (77.8%)	7,620 (63.8%)	442 (69.4%)
<i>OCS</i>	7,479 (23.0%)	3,087 (24.4%)	1,742 (24.1%)	2,502 (21.0%)	148 (23.2%)
<i>Theophylline</i>	664 (2.0%)	305 (2.4%)	128 (1.8%)	220 (1.8%)	11 (1.7%)
Asthma exacerbations (past year)⁴	1,896 (5.8%)	750 (5.9%)	430 (6.0%)	674 (5.6%)	42 (6.6%)
Person level measures					
Number of asthma patients treated	32,454 (100.0%)	12,654 (100.0%)	7,227 (100.0%)	11,936 (100.0%)	637 (100.0%)
Number of new ICS+LABA users	14,571 (44.9%)	5,211 (41.2%)	3,395 (47.0%)	5,819 (48.8%)	615 (96.5%)

	Overall N (%)	Advair Diskus N (%)	Advair HFA ¹ N (%)	Symbicort N (%)	Zenhale ² N (%)
Age (Median, IQR)	52.3 (42.3-60.3)	53.3 (44.4-60.7)	52.1 (41.5-59.9)	51.6 (40.8-60.2)	48.6 (38.9-59.8)
Males	10,741 (33.1%)	4,191 (33.1%)	2,433 (33.7%)	3,902 (32.7%)	215 (33.8%)
Prescribed Treatment Step⁵					
<i>Step 3</i>	743 (2.3%)	598 (4.7%)	77 (1.1%)	55 (0.5%)	13 (2.0%)
<i>Step 4</i>	21,455 (66.1%)	7,410 (58.6%)	2,530 (35.0%)	11,230 (94.1%)	285 (44.7%)
<i>Step 5</i>	10,256 (31.6%)	4,646 (36.7%)	4,620 (63.9%)	651 (5.5%)	339 (53.2%)
LTC resident	326 (1.0%)	139 (1.1%)	124 (1.7%)	*	≤5
Urban residence	28,503 (87.8%)	11,112 (87.8%)	6,392 (88.4%)	10,396 (87.1%)	603 (94.7%)
Socioeconomic status					
<i>Q1 (lowest)</i>	13,163 (40.6%)	5,196 (41.1%)	3,066 (42.4%)	4,663 (39.1%)	238 (37.4%)
<i>Q2</i>	7,454 (23.0%)	2,931 (23.2%)	1,654 (22.9%)	2,717 (22.8%)	152 (23.9%)
<i>Q3</i>	5,064 (15.6%)	1,936 (15.3%)	1,135 (15.7%)	1,894 (15.9%)	99 (15.5%)
<i>Q4</i>	3,923 (12.1%)	1,496 (11.8%)	799 (11.1%)	1,535 (12.9%)	93 (14.6%)
<i>Q5 (highest)</i>	2,695 (8.3%)	1,039 (8.2%)	531 (7.3%)	1,073 (9.0%)	52 (8.2%)

¹ HFA = 1,1,1,2-tetrafluoroethane (propellant)

² Zenhale added to the provincial drug formulary in February 2012

³ Over fiscal year 2012/13

⁴ Defined as hospitalization or ED visits related to asthma

⁵ Based on calculated ICS daily dose (details in Appendix D)

*In accordance with ICES privacy policies, cells ≤5 have been suppressed. In the case that the number of users was ≤5, all relevant measures have been suppressed as well, in order to avoid residual disclosure of small cells.

Exhibit 14: Baseline characteristics of asthma patients ages 66+ treated with provincially-funded ICS+LABA combination products in Ontario, by product, fiscal year 2012/13

	Overall N (%)	Advair Diskus N (%)	Advair HFA ¹ N (%)	Symbicort N (%)	Zenhale ² N (%)
Prescription level measures					
Number of puffs dispensed, per user Median (IQR)	480.0 (240.0-780.0)	420.0 (180.0-660.0)	600.0 (240.0-1,080.0)	600.0 (240.0-1,080.0)	240.0 (120.0-720.0)
Number of puffers dispensed, per user Median (IQR)	6.0 (2.0-10.0)	7.0 (3.0-11.0)	5.0 (2.0-9.0)	5.0 (2.0-9.0)	2.0 (1.0-6.0)
Cost of ICS+LABA prescriptions, per user Mean (SD)³	708.7 (528.8)	843.4 (564.4)	774.8 (549.0)	530.6 (411.9)	412.4 (401.9)
ODB plan					
<i>Seniors</i>	74,118 (95.5%)	30,667 (95.4%)	14,823 (92.9%)	27,538 (97.0%)	1,090 (97.9%)
<i>ODSP</i>	355 (0.5%)	169 (0.5%)	72 (0.5%)	108 (0.4%)	6 (0.5%)
<i>Ontario Works</i>	25 (0.0%)	*	≤5	≤5	0 (0.0%)
<i>LTC</i>	1,943 (2.5%)	797 (2.5%)	780 (4.9%)	*	≤5
<i>Homes for Special Care</i>	6 (0.0%)	≤5	≤5	0 (0.0%)	0 (0.0%)
<i>Trillium</i>	208 (0.3%)	94 (0.3%)	39 (0.2%)	*	≤5
<i>Home Care</i>	948 (1.2%)	404 (1.3%)	232 (1.5%)	302 (1.1%)	10 (0.9%)
Asthma maintenance therapy (past year)					
<i>ICS</i>	9,706 (12.5%)	3,503 (10.9%)	2,566 (16.1%)	3,233 (11.4%)	404 (36.3%)
<i>LABA</i>	863 (1.1%)	351 (1.1%)	140 (0.9%)	323 (1.1%)	49 (4.4%)
<i>LAMA</i>	28,486 (36.7%)	13,748 (42.8%)	6,312 (39.6%)	8,138 (28.7%)	288 (25.9%)
<i>LTRA</i>	47 (0.1%)	23 (0.1%)	10 (0.1%)	13 (0.0%)	≤5
<i>SAMA</i>	4,995 (6.4%)	2,109 (6.6%)	1,582 (9.9%)	1,253 (4.4%)	51 (4.6%)
<i>SABA</i>	44,911 (57.9%)	19,600 (61.0%)	10,874 (68.2%)	13,757 (48.5%)	680 (61.1%)
<i>OCS</i>	18,361 (23.7%)	7,891 (24.5%)	4,091 (25.6%)	6,050 (21.3%)	329 (29.6%)
<i>Theophylline</i>	2,444 (3.1%)	1,250 (3.9%)	466 (2.9%)	700 (2.5%)	28 (2.5%)
Asthma exacerbations (past year) ⁴	1,640 (2.1%)	642 (2.0%)	397 (2.5%)	557 (2.0%)	44 (4.0%)
Person level measures					

	Overall N (%)	Advair Diskus N (%)	Advair HFA ¹ N (%)	Symbicort N (%)	Zenhale ² N (%)
Number of asthma patients treated	77,603 (100.0%)	32,153 (100.0%)	15,951 (100.0%)	28,386 (100.0%)	1,113 (100.0%)
Number of new ICS+LABA users	17,664 (22.8%)	6,776 (21.1%)	4,203 (26.3%)	7,282 (25.7%)	1,024 (92.0%)
Age (Median, IQR)	75.7 (70.5-81.8)	76.1 (70.8-82.0)	76.9 (71.1-83.2)	74.8 (70.0-80.8)	73.9 (69.5-79.1)
Males	30,477 (39.3%)	12,989 (40.4%)	5,963 (37.4%)	11,127 (39.2%)	398 (35.8%)
Prescribed Treatment Step⁵					
Step 3	5,566 (7.2%)	4,629 (14.4%)	651 (4.1%)	244 (0.9%)	42 (3.8%)
Step 4	54,050 (69.6%)	19,537 (60.8%)	7,223 (45.3%)	26,756 (94.3%)	534 (48.0%)
Step 5	17,987 (23.2%)	7,987 (24.8%)	8,077 (50.6%)	1,386 (4.9%)	537 (48.2%)
LTC resident	3,296 (4.2%)	1,374 (4.3%)	1,328 (8.3%)	585 (2.1%)	9 (0.8%)
Urban residence	68,122 (87.8%)	28,218 (87.8%)	14,045 (88.1%)	24,842 (87.5%)	1,017 (91.4%)
Socioeconomic status					
Unknown	*	104 (0.3%)	*	89 (0.3%)	≤5
Q1 (lowest)	16,328 (21.0%)	6,958 (21.6%)	3,631 (22.8%)	5,512 (19.4%)	227 (20.4%)
Q2	16,591 (21.4%)	6,907 (21.5%)	3,589 (22.5%)	5,859 (20.6%)	236 (21.2%)
Q3	15,308 (19.7%)	6,317 (19.6%)	3,161 (19.8%)	5,618 (19.8%)	212 (19.0%)
Q4	14,906 (19.2%)	6,157 (19.1%)	2,907 (18.2%)	5,606 (19.7%)	236 (21.2%)
Q5 (highest)	14,218 (18.3%)	5,710 (17.8%)	2,606 (16.3%)	5,702 (20.1%)	200 (18.0%)

¹ HFA = 1,1,1,2-tetrafluoroethane (propellant)

² Zenhale added to the provincial drug formulary in February 2012

³ Over fiscal year 2012/13

⁴ Defined as hospitalization or ED visits related to asthma

⁵ Based on calculated ICS daily dose (details in Appendix D)

*In accordance with ICES privacy policies, cells ≤5 have been suppressed. In the case that the number of users was ≤5, all relevant measures have been suppressed as well, in order to avoid residual disclosure of small cells.

Among the 111,064 asthma patients treated with ICS+LABA combination products in fiscal year 2012, Advair was the most commonly used product among all age groups.

Summary of Findings for Exhibit 12, Exhibit 13 and Exhibit 14

1. Among the 1,007 youth (aged 12-17) asthma patients treated with an ICS+LABA combination product in fiscal 2012, 41.2% (N=415) were dispensed Symbicort, 29.4% (N=296) were dispensed Advair HFA, 25.8% (N=260) were dispensed Advair Diskus, and 3.6% (N=36) were dispensed Zenhale.
2. Among the 32,454 younger adult (aged 18-64) asthma patients treated with an ICS+LABA combination product in fiscal 2012, 39.9% (N=11,936) were dispensed Symbicort, 39.0% (N=12,654) were dispensed Advair Diskus, 22.3% (N=7,227) were dispensed Advair HFA, and 2.0% (N=637) were dispensed Zenhale.
3. Among the 77,603 older adult (ages 65+) asthma patients treated with an ICS+LABA combination product in fiscal 2012, 41.4% (N=32,153) were dispensed Advair Diskus, 36.6% (N=28,386) were dispensed Symbicort, 20.6% (N=15,951) were dispensed Advair HFA, and 1.4% (N=1,113) were dispensed Zenhale.
4. In fiscal year 2012, the median number of puffs dispensed per user was the same and highest for Advair HFA and Symbicort users for all age groups (youth: 240, younger adults: 480; older adults: 600) and lowest for Zenhale users (youth: 120; younger adults: 240; older adults: 240). The median number of puffers dispensed per user ranged from 1 (Zenhale) to 2 (Advair Diskus, Advair HFA, and Symbicort) in youth, 2 (Zenhale) to 5 (Advair Diskus) in younger adults, and 2 (Zenhale) to 7 (Advair Dikus) in older adults.
5. In fiscal year 2012, 10.1% (N=102) of youth patients experienced asthma exacerbations in the previous one year, compared to 5.8% (N=1,896) of younger adult and 2.1% (N=1,640) of older adult patients.
6. Zenhale users were more likely than other ICS+LABA combination users to have utilized ICS asthma maintenance therapy in the previous year (youth 47.2% vs. 26.3%; younger adults 43.0% vs. 17.3%; older adults 36.3% vs. 12.2%). Youth, younger adult and older adult ICS/LABA users had high rates of SABA maintenance therapy use in the previous year regardless of ICS+LABA combination product used (70.2%, 71.7% and 57.9%, respectively).
7. In youth, the majority of Zenhale users had the highest prescribed treatment step, Step 5 (52.8%), whereas the majority of youth using other ICS+LABA combination products had Step 4 (Advair Diskus 70.8%, Advair HFA 58.1%, and Symbicort 93.7%). In younger adults, the majority of Advair HFA and Zenhale users had the highest prescribed treatment step, Step 5 (63.1%), whereas the majority of younger adults using Advair Diskus (58.6%) and Symbicort (94.1%) had Step 4. In older adults, Zenhale and Advair HFA users had similar proportions of patients of prescribed treatment step 4 (45.5%) and Step 5 (50.5%), whereas the majority of Advair Diskus (60.7%) and Symbicort (94.3%) users had Step 4.
8. In older adults, Advair users were more likely to be residents of long-term care facilities (4.3% among Advair Diskus users and 8.3% among Advair HFA users vs. 2.1% among Symbicort users and 0.82% among Zenhale users).

Patterns of Asthma therapy use and discontinuation among new users

Exhibit 15: Patterns of asthma therapy use among new users of provincially-funded ICS+LABA combination and dual therapy in Ontario, April 2008 to March 2013, by therapy and age group (using 180 day window to define continuous use)

	Age 12-17	Age 18-65		Age 66+	
	Combination Therapy	Combination Therapy	Dual Therapy	Combination Therapy	Dual Therapy
Number with only 1 prescription (%)	50-60%	40-50%	0%**	40-50%	0%**
% Adherent to therapy after 1 year	20-30%	40-50%	30-40%	40-50%	40-50%
Median time to discontinuation*	3-6 months	9-12 months	6-9 months	9-12 months	6-9 months

*Among those prescribed >1 prescription

**Note: >1 prescription required as definition of continuous use in definition for dual therapy

Individuals with asthma newly treated with ICS+LABA combination therapy differ from those treated with dual therapy in regards to urban residence, LTC residency, COPD diagnosis, concomitant asthma therapy use and use of other asthma therapy prior to initiation of ICS+LABA. After adjusting for patient characteristics and performing a sensitivity analysis, adherence to therapy did not differ significantly between combination therapy and dual therapy among younger adults and older adults.

Summary of Findings for Exhibit 15

1. Among patients with asthma initiating ICS+LABA therapy, the majority initiated combination therapy (>90%). About 50-60% of youth asthma patients, 40-50% of younger adult patients, and 40-50% of older adult patients received only one prescription before discontinuing therapy.
2. Among patients who continued ICS+LABA therapy:
 - a. The majority of ICS+LABA users had prescribed treatment step 4 across all age groups.
 - b. More dual therapy users had a COPD diagnosis compared to combination therapy users among younger adult (60-70% and 40-50%, respectively) and older adult (80-90% and 60-70%, respectively) age groups.
 - c. The prevalence of triple therapy (ICS + LABA + LAMA) was low among youth asthma patients (<1%), moderate among young adult patients (20-30%) and highest among older adult patients (40-50%).
 - d. Concomitant therapy utilization in younger and older adults was higher among patients on dual therapy compared to combination therapy. The most common concomitant asthma therapy was SABAs.
 - e. Over two thirds of asthma patients initiating combination therapy received asthma therapy in the previous year. Prior use of asthma therapies was generally higher among dual therapy users compared to combination therapy users for all asthma agents.
 - f. Adherence to ICS+LABA combination products after one year was lowest among youth asthma patients (20-30%). Adherence after one year was lower among patients on dual therapy compared to combination therapy in younger adults (30-40% and 40-50%, respectively) and older adults (40-50% and 40-50%, respectively).

Exhibit 16: Patterns of asthma therapy use among new users or provincially-funded ICS+LABA combination and dual therapy in Ontario, April 2008 to March 2013, by product and age group (using 180 day window to define continuous use)

	Age 12-17		Age 18-65		Age 66+	
	Advair	Symbicort	Advair	Symbicort	Advair	Symbicort
Number with only 1 prescription (%)	50-54%	60-64%	40-44%	45-49%	35-39%	45-49%
% Adherent to therapy after 1 year	20-24%	25-29%	40-44%	35-39%	45-49%	40-44%
Median time to discontinuation*	3-6 months	6-9 months	9-12 months	9-12 months	12-15 months	9-12 months

*Among those prescribed >1 prescription

New users of Advair may be more likely to receive multiple prescriptions, receive prior asthma therapies, be dispensed triple therapy and concomitant asthma therapies, have a COPD diagnosis and be a LTC resident compared to new Symbicort users. After adjusting for patient characteristics and performing a sensitivity analysis, adherence to therapy differed slightly between ICS+LABA combination among older adults, but not among younger adults and youth. The clinical relevance of the observed difference in the older adult population is unknown.

Summary of Findings for Exhibit 16

1. Over half of new ICS+LABA users initiated Advair therapy among youth aged 12-17 (50-54%), young adults aged 18-65 (60-70%) and older adults aged 66 and older (60-70%). Among all age groups, a higher proportion of new Symbicort users discontinued therapy after only one prescription compared to new Advair users (youth: 60-64% vs. 50-54%; young adults: 45-49% vs. 40-44%; and older adults: 44-49% vs. 35-39%, respectively).
2. Among patients receiving multiple prescriptions for an ICS+LABA combination product:
 - a. The majority of young adult and older adult patients were female compared to about half among the youth population.
 - b. In older adults, the proportion of long term care residents using Advair was twice the proportion for Symbicort users.
 - c. The prevalence of triple therapy was higher for Advair users than Symbicort users for both younger (20-30% and 10-20%, respectively) and older (40-50% and 20-30%, respectively) adult populations.
 - d. The most common concomitant asthma therapy among all age groups and combination product users was SABAs, with higher usage rates among Advair users compared to those using Symbicort.
 - e. Advair patients were more likely than Symbicort patients to have tried other therapies in the past year.
 - f. More Advair users had a COPD diagnosis compared to Symbicort users among young adult (40-50% and 30-40%, respectively) and older adult (70-80% and 50-60%, respectively) age groups.
 - g. After adjusting for patient characteristics, adherence to therapy did not differ between Advair and Symbicort users among youth and young adults.
 - h. Among older patients, users were slightly more adherent to Advair compared to Symbicort, this difference was not significant. However, when performing a sensitivity analysis, using a more restrictive continuous use definition and adjusting for important confounders, ICS+LABA combination users were found to be significantly more adherent to Advair compared to Symbicort ($p < 0.0001$).

Key Findings

National and Provincial Trends in ICS+LABA Prescribing

ICS+LABA combination products are the second most commonly prescribed anti-inflammatory and bronchodilator agents in Canada, with 1.1 million prescriptions dispensed in the fourth quarter (Q4: October to December) of 2013. Over half (56.5%; 600,340 prescriptions; Q4 2013) of all prescriptions for ICS+LABA combination products dispensed in Canada were for Advair. Ontario has the second-highest utilization rate of provincially funded ICS+LABA combination products (7,127 prescriptions dispensed per 100,000 eligible population vs. national average of 5,063 prescriptions per 100,000 eligible population in Q4 2013). Total national expenditures on ICS+LABA combination products in the last quarter of 2013 were \$129.3 million, 52.3% of overall national spending on anti-inflammatory/bronchodilator products (\$247.2 million, Q4 2013).

Use of ICS+LABA Combination Products in Ontario

Just over half (53%) of all ICS+LABA combination products dispensed in Ontario are paid for through the Ontario Public Drug Program (OPDP), while 38% were covered through private health insurance. In 2012, ICS+LABA combination products were the third most commonly dispensed therapy among youth aged 12 to 17 (following SABA and ICS therapies), the second most commonly dispensed therapy among adults aged 18 to 64 (following SABA therapy) and the most commonly dispensed therapy among older adults (aged 65 years and older) public drug plan beneficiaries with asthma. Among individuals with asthma, the number of ICS+LABA combination product users has increased nearly 23-fold across all age groups, between 2000 and 2012. By 2012, among individuals with asthma, the majority (71%) of ICS+LABA combination products were being used by older adults. The rate of ICS+LABA combination product users has also increased over time across all age groups (between 2000 and 2013); however a decline in the rate of users among youth and young adults was observed between 2011 and 2013. Advair was the most utilized ICS+LABA combination therapy product and had the highest average cost per user among asthma users aged 12-17 (54.2% and \$362.1 respectively), 18-64 (59.7% and \$697.9, respectively) and 65 and older (60.6%; \$791.3, respectively) in 2012. Symbicort was the second most utilized combination product in 2012. By 2012, the overall cost of provincially funded ICS+LABA combination products dispensed to asthma patients in Ontario was \$79.2 million.

Characteristics of ICS+LABA Users with Asthma in Ontario in 2012

In fiscal year 2012, 111,064 asthma patients aged 12 and older, received provincially-funded ICS+LABA combination products in Ontario. Advair (Diskus and HFA) was the most commonly used product in all age groups. Asthma patients dispensed ICS+LABA products through the OPDP were typically over 65 years of age (69.9%) and lived in urban locations (87.8%). The majority of asthma therapy users aged 18 and older were female (62.5%) compared to those younger than 18 years of age (47.3%). Youth (aged 12-17) were more likely to be new users of ICS+LABA therapy compared to younger adults (aged 18-65) and older adults (over 65 years of age) (64.2%, 44.9% and 22.8%, respectively). Youth users (aged 12-17) also experienced more asthma exacerbations in the previous one year, compared to younger adults (aged 18-65) and older adults (over 65 years of age) (10.1%, 5.8% and 2.1%, respectively). Among older adults, Advair users were more likely to be residents of long-term care facilities compared to Symbicort

and Zenhale users (5.6%, 2.1% and 0.8%, respectively).

Patterns of Use and Discontinuation of Asthma therapy in Ontario

Among asthma patients initiating ICS and LABA therapy between 2008 and 2013, less than 10% initiated dual therapy (concurrent single-agent ICS and LABA products). Among the youth (aged 12-17) asthma patients initiating ICS+LABA combination therapy, and 20-30% were still on therapy after 1 year of initiation. Adults treated with combination ICS+LABA products differed from those treated with dual therapy, in regards to urban residence, LTC residency, COPD diagnosis, concomitant asthma therapy use and use of other asthma therapy prior to initiation of ICS+LABA. Notably, more dual therapy users had a COPD diagnosis compared to combination therapy users among both young adults (60-70% and 40-50%, respectively) and older adults (80-90% and 60-70%, respectively). Prior use of asthma therapy was generally higher among dual therapy users compared to combination therapy users for all asthma agents. Younger adults were more adherent to combination therapy compared to dual therapy, however this did not differ significantly after adjusting for important confounders. Among older adults, adherence to combination therapy and dual therapy differed depending on the definition of continuous use, however after adjusting for potential confounders no significant difference in adherence was observed.

Among the youth, younger adult and older adult asthma patients newly initiating ICS+LABA combination therapy between 2008 and 2013, the majority started on an Advair product (55-60%, 60-64% and 60-64%, respectively) compared to a Symbicort product. Zenhale use was not captured during our study period. New users of Advair were more likely to receive multiple prescriptions, receive prior asthma therapies, and be dispensed triple therapy and concomitant asthma therapies compared to new Symbicort users, indicating more severe disease among Advair users. More Advair users had a COPD diagnosis compared to Symbicort users among young adults (45-49% and 35-39%, respectively) and older adults (70-74% and 55-59%, respectively). Adherence to ICS+LABA combination therapy did not differ significantly between Symbicort and Advair therapy among youth. Among young adults, ICS+LABA users were slightly more adherent to Advair compared to Symbicort therapy, however the difference was not significant after adjusting for important confounders. Among older patients, new ICS+LABA combination therapy users were slightly more adherent to Advair compared to Symbicort, this difference was not significant. However, when performing a sensitivity analysis, using a more restrictive continuous use definition and adjusting for important confounders, older ICS+LABA combination users were found to be slightly but statistically significantly more adherent to Advair compared to Symbicort ($p < 0.0001$). The clinical relevance of this difference is likely minimal.

Cyclic Trends

We observed a major cyclic trend in rates of provincially-funded use of ICS+LABA combination products in British Columbia, with rates being lowest in the first quarter of the year and highest at the end of the year. A similar trend exists in Manitoba, with rates being highest in the first quarter of the year. British Columbia and Manitoba have more expanded public drug coverage among the younger population through their PharmaCare programs, and therefore it is likely that this phenomenon is being driven by patterns of deductible payments and associated stockpiling of drugs near the end of the coverage period (calendar year [January – December] in British Columbia, and fiscal year [April – March] in Manitoba). Smaller cyclic trends were observed in other provinces, which may reflect seasonal influences on respiratory therapy management.

Health Equity

Stratified analyses suggest that there isn't a major equity issue in access to these medications by age or gender. ICS+LABA utilization was higher among older patients and more common among women in younger and older adults (approximately 66.9% and 60.7%, respectively). This aligns with the higher prevalence of a COPD diagnosis among older individuals and among females. Among youth, slightly more users were male (52.7%).

Limitations

Data Availability

Several limitations to availability of data warrant discussion:

1. No data is available for the Territories, and therefore all analyses are restricted to inter-provincial comparisons.
2. IMS Geographic Prescription Monitor (GPM¹²) does not collect patient-level data, and therefore information on privately funded prescriptions is only available at the prescription and unit (e.g. tablet) level.
3. Data on the number of individuals eligible for public drug coverage was estimated based on prescription trends (where available) and public annual reports. Therefore, these may slightly underestimate the true size of the public beneficiary population; however, this does reflect the number of active beneficiaries (e.g. those filling at least one prescription over a given year) each year.
4. A diagnosis of asthma and COPD rely on administrative databases. Although these databases have been validated, and have high sensitivity and specificity, some misclassification of diagnoses is possible. In particular, some of the individuals treated with ICS+LABA combination products with no indication of COPD or asthma may in fact have minor disease that has not yet

been identified in the administrative data.

5. Our definition of the prescribed treatment step is limited to the information available through administrative data holdings. This definition was derived from the GINA prescribed treatment step⁶ as well as from clinical input. The calculated daily dose on ICS prescriptions in dual therapy and combination therapy were used to categorize treatment step. As a result, we may be underestimating the true treatment step by not taking into account other therapies used with ICS and LABA products.
6. Seasonal changes may impact the persistence on therapy for individuals with asthma.

Generalizability

1. All analyses using IMS Geographic Prescription Monitor (GPM¹²) data reflect medication use among the entire population; however, we are unable to stratify these analyses by indication for therapy.
2. Analyses of prescribing trends conducted among public drug beneficiaries were restricted to those aged 12 and older, and therefore are generalizable to only this population.

Adherence

All data used in these analyses are based on dispensing patterns, and therefore we do not know whether people took the medications. This is particularly questionable among the population of individuals who only received one prescription for an ICS+LABA combination product. It is possible that they never tried the medication, or tried it and did not finish their initial course of therapy. For this reason, we looked at characteristics among ICS+LABA users who were dispensed more than one prescription.

Review of the Observational Literature

The safety and efficacy of ICS+LABA combination products as established in randomized controlled trials is summarized in the report by the Systematic Review Team. However, these trials typically have strict inclusion criteria, and do not generally conduct head-to-head comparisons between ICS+LABA combination products. A review of the observational literature comparing ICS+LABA combinations in the treatment of asthma will help provide real-world estimates of safety and effectiveness of these products.

Objectives

We conducted a rapid review of the observational literature to investigate the comparative safety and effectiveness of ICS+LABA combination products compared either to other combination products, or to individuals taking dual therapy of ICS and LABA single agent products for the treatment of asthma.

Methods

Search Strategy

We performed a Medline search for all literature published between 1996 and July 2014. Search terms included budesonide, formoterol, fluticasone, salmeterol, Advair, Symbicort, and combination inhaled corticosteroid and long-acting beta agonist. Overall, 177 abstracts were reviewed, and potentially relevant articles were obtained in full text. Additionally, 46 reviews had their citations reviewed to search for any additional studies. Two studies submitted through Evidence Submission Packages were included but they were also found in our review.

Inclusion Criteria:

- English Language
- Published between 1996 and July 2014
- Asthma patient population
- Safety or Effectiveness outcome reported
- Comparison between either:
 - Two different ICS+LABA combination products; or
 - One ICS+LABA combination product and dual ICS + LABA therapy

Overall 9 studies were included in the final review. 6 of these studies compared effectiveness, safety and/or adherence of budesonide/formoterol to fluticasone/salmeterol products. Two studies looked at prescribing appropriateness and one compared combination therapy to concurrent therapy. See Table 1 for a summary of all included studies.

Results

Budesonide/formoterol vs. fluticasone/salmeterol

We identified 6 observational studies that compared the effectiveness and/or safety of budesonide/formoterol combination products (BFC) to fluticasone/salmeterol combination products (FSC). Outcomes investigated in these studies included rates of exacerbations, asthma control, and adherence.

Asthma Exacerbations and Hospitalizations

Four studies compared rates of exacerbations between users of BFC vs. FSC.⁷⁻¹⁰ All four studies were funded by AstraZeneca (the manufacturer of the BFC product).

Two studies conducted using UK data found no overall difference in exacerbations between the two exposure groups.^{9,10} The first study by Price et al. was a matched cohort study among users of either BFC or FSC in a large database. The mean age of patients included in this study was 53.4 years, and after matching 3:1 (N=1,146 FSC and N=382 BFC) patients were similar with respect to most demographic characteristics and baseline comorbid conditions.⁹ This study found no significant differences in rates of exacerbation based on hospitalization events within 12 months between groups (adjusted rate difference of 0.02; 95% CI -0.03 to 0.07). The second UK study by Suissa et al. was a cohort study using similar data as Price et al., this study had a larger sample size (N=16,157 FSC and N=6,918 BFC) due to the implementation of a new-user design.¹⁰ This study also found no difference between the two products after controlling for confounders using a propensity score design (Rate ratio = 1.01 95% CI 0.92 to 1.10). In this study exacerbations were assessed by looking at hospitalizations. Not all of the studies found no difference between products. A study conducted by Aballea et al. (N=982 FSC and N=1,456 BFC) utilizing German claims data found a higher rate of exacerbations, based on hospitalization, among users of FSC (0.1995 vs. 0.103, p= 0.0018), this was a crude result that was not found to be significant when adjusted for the post-index year.⁷ A similar result was found by Blais et al. (N=1,264 FSC and N=1,264 BFC) in a Quebec based matched cohort study that found BFC users were less likely to have severe exacerbations (Rate ratio = 0.72; 95% CI 0.54-0.96).⁸

Key Findings

Although there are 4 large population-based cohort studies comparing BFC to FSC, the findings from these studies are not consistent. This may be driven by the differential follow-up and design in each study. Both studies conducted in the UK^{9,10} reported no significant difference in rates of exacerbations. Significant differences between treatment groups, favouring BFC, were found among the two studies conducted outside of the UK.^{7,8} Results of these studies should be interpreted with caution due to the possible impact of systematic differences in comparison groups leading to bias.

Asthma Control and SABA use

Only 4 of the included studies reported on asthma control.⁷⁻¹⁰ All 4 studies used SABA utilization in some form as the surrogate to assess control using different definitions to define control. Price et al.

found that users of BFC were more likely to achieve overall asthma control (odds ratio = 1.56 (95% CI 1.14 to 2.14)) and have lower SABA utilization (odds ratio = 0.74 (95% CI 0.60 to 0.91)).⁹ Price et al. defined control on a combination of SABA use, occurrence of exacerbation, use of OCS, and change in therapy. Abella et al. found a similar outcome when reporting crude results, with 68.3% of BFC users achieving full control success versus 62.5% of FSC users ($p=0.0060$) based on SABA use per day.⁷ The adjusted estimates found a similar result with BFC users more likely to achieve control (odds ratio = 1.44 $p=0.0003$). Their study defined success as full or partial control based on changes in therapy and SABA utilization. Blais et al. also explored SABA utilization and found that BFC users were less likely to use SABA (mean difference = -1.1; 95% CI -1.7 to -0.5).⁸ Suissa et al. was the only study to find no difference between agents in terms of SABA use (Rate ratio = 0.98; 95% CI 0.94-1.01). Suissa et al. and Blais et al. both utilized SABA utilization as the only assessment of asthma control.

Two additional studies were found using the same population in Italy. One study¹¹ reports the initial cross-sectional analysis and the second¹² reports a one-year follow up on the same patients. This study looks at a group of patients receiving treatment from specialists. These studies did not report the head to head comparison between BFC and FSC, rather they compared to a third product that is not available in Canada. Both of these studies report superiority of the third product.

Key Findings

Only 4 large population-based cohort studies comparing BFC to FSC in terms of asthma control. Three of the included studies showed better control with the use of BFC. A fourth study showed no difference between agents. Use of SABA is a good indicator of asthma control but varying definitions between studies does not allow for easy comparability of studies.

Adherence and Appropriate Use

Only two of the studies included assessed adherence to therapy. Price et al. found that users of BFC were more likely to be adherent (odds ratio = 1.40 (95% CI 1.13 to 1.73)) to therapy.⁹ In contrast, Suissa et al. found no difference between agents in terms of persistence at 1 year of follow-up, with a mean duration of about 5 months.¹⁰

Two studies investigating comparative appropriate prescribing of ICS/LABA products in asthma patients were identified.^{13, 14} Both studies looked at US patient utilizing claims data. The first study by Blanchette et al. (N=14,788 FSC and N=1,417 BFC) was a cohort study of patients who were new users of either BFC or FSC.¹³ This study found that patients prescribed BFC were more likely to have met at least 1 criteria of appropriateness (odds ratio= 1.79; 95% CI 1.60-2.00). A similar finding was found by Ye et al. (N=23,238 FSC and N=992 BFC) pointing to more appropriate use among BFC users (odds ratio= 2.01; 95% CI 1.76-2.30).¹⁴ Both studies found a relatively low level of overall appropriate use, with Blanchette et al. finding an overall appropriateness of 39.2% and Ye et al. finding an overall appropriateness for 37.6%. Both studies point to impact of comorbidity, specialist prescriber, co-medications and geographic variation as

significant factors of appropriate prescribing of ICS/LABA products.

Key findings

Only two studies looked at adherence to therapy between ICS/LABA agents, with one study finding a significant differences in favour of BFC while a second study finding no difference between agents. Two cohort studies that reported comparative appropriateness of ICS+LABA combination therapy showed possible differences in appropriate prescribing. In general, it appears that differences in appropriateness may exist in the US, with a higher likelihood of inappropriate prescribing occurring with FSC. Overall appropriate prescribing was found to be around 37%-39%.

Combination vs. Concurrent Therapy with ICS and LABA

We identified only one observational study that compared the use of ICS+LABA combination products (FSC) and dual therapy. This study was conducted in Quebec, and investigated adherence, exacerbations, and SABA use.¹⁵ This study found that those using combinations ICS/LABA products were 17% less likely to stop therapy when compared to those that used two concurrent ICS and LABA products. The rate of exacerbations was not found to differ between groups.

Conclusions

Comparative observational studies of ICS+LABA combination products suggest that BFC and FSC are largely comparable products as it relates to exacerbations, asthma control and adherence to therapy. There is some evidence to suggest that BFC may be superior to FSC for some measures of control and exacerbation, however the quality and design of these studies could influence these findings. Any differences in reported effectiveness should be interpreted with caution. There were no studies identified that assessed safety differences between agents in this population. Only one study compared combination product and dual therapy. This study suggested that combinations products may lead to improved adherence when compared to concurrent therapy.

Overall, the evidence in this area from observational studies is inconsistent and of varying quality. This body of research does not suggest any clinically relevant systematic difference between ICS+LABA combination products for any of the outcomes investigated.

Appendix A: Summary of Included Studies

Study Author	Study Design	Population	Comparison	Outcomes	Key Findings	Strengths/Limitations
Aballea et al. ⁷	Retrospective Cohort Study	Germany 1,456 BFC 982 FSC	BFC vs. FSC	Treatment Success (SABA use, change of therapy, addition of therapy) Asthma Exacerbations Hospitalizations	<ul style="list-style-type: none"> • BFC showed evidence of higher chance of treatment success • The use of SABAs was found to be no different but higher OCS was found among FSC users • FSC users had significantly more exacerbations but no difference in the number of referrals due to asthma • BFC use was found to be less costly than FSC use 	<p>Real-world data and clinically relevant outcomes</p> <p>High-level of non-adherence in the population may bias results</p> <p>Primary outcome is composite of claims</p> <p>Industry-funded</p>

Study Author	Study Design	Population	Comparison	Outcomes	Key Findings	Strengths/Limitations
Allegra et al. ¹¹	Cross-sectional	Italy 454 BFC (extra fine) 453 BFC 473 FSC	BFC vs. FSC	Asthma Control (controlled, partial, and uncontrolled) Healthcare utilization (outpatient and hospitalization) Mean ICS dose Quality of Life (EQ-5D)	<ul style="list-style-type: none"> • Beclomethasone formulation (not available in Canada) was found to have better quality of life and improved asthma control • BFC users (both formulation) used lower equivalent doses of ICS 	<p>Real-world data with clinical data on variables such as FEV and smoking</p> <p>Cross-sectional design does not allow for true comparison of treatments</p> <p>The data only comes from patients who are receiving treatment from a specialist</p>
Blais et al. ⁸	Matched Cohort Study	Quebec 1,264 BFC 1,264 FSC	BFC vs. FSC	ED Visits , hospitalizations due to asthma OCS and SABA use Specialist and ambulatory visits	<ul style="list-style-type: none"> • BFC users were less likely to have ED visit or hospitalization • BFC users were more likely to use OCS • No differences were found in the number of medical and specialist visits 	<p>Real-world data and clinically relevant outcomes</p> <p>Asthma diagnosis is difficult to validate</p> <p>SABA use is estimated based on rate of filling</p> <p>Industry-funded</p>

Study Author	Study Design	Population	Comparison	Outcomes	Key Findings	Strengths/Limitations
Blanchette et al. ¹³	Cohort Study	USA 1,417 BFC 14,788 FSC	BFC vs. FSC	Appropriate Use	<ul style="list-style-type: none"> • 39.2% of patients met 1 or more criteria for appropriate use • BFC users were more likely to be used appropriately compared to FSC users • Users treated by specialists were more likely to have appropriate use 	<p>Real-world data with a large sample size</p> <p>Asthma diagnosis and severity is difficult to validate</p> <p>No clinical data to validate the appropriateness of use based on disease severity</p> <p>Industry-funded</p>
Marceau et al. ¹⁵	Matched cohort Study	Quebec 2,559 Combination 2,559 Concurrent	Combination products vs. concurrent therapy	<p>Persistence and adherence</p> <p>Exacerbations</p> <p>SABA use</p>	<ul style="list-style-type: none"> • Low persistence and adherence overall • Patient on combination products were more persistent and adherent to therapy • Patients using combination products were less likely to have exacerbations 	<p>Real-world data with a large sample size</p> <p>No information on disease severity and clinical markers</p> <p>Unknown utilization and dosing of medications</p>

Study Author	Study Design	Population	Comparison	Outcomes	Key Findings	Strengths/Limitations
Price et al. ⁹	Matched Cohort study	UK 392 BFC 1,146 FSC	BFC vs. FSC	Severe Exacerbations Asthma control and SABA use Adherence Economic analysis (not included)	<ul style="list-style-type: none"> • BFC was as effective in preventing severe exacerbations as FSC • Switching from FSC to BFC was associated with better asthma control and lower SABA use • BFC was associated with better adherence after switching from FSC 	<p>Real-world data with clinical information and large sample size</p> <p>Comparing switched to non-switched patients introduces bias that matching cannot control for</p>
Suissa et al. ¹⁰	Cohort Study	UK 6,918 BFC 16, 157 FSC	BFC vs. FSC	Adherence to combination therapy Switching to other product Hospitalizations and doctor visits due to asthma Use of other asthma treatment (SABA, OCS, other treatment)	<ul style="list-style-type: none"> • Similar effectiveness between BFC and FSC • No difference in hospitalization of doctor visits between products • BFC was associated with fewer prescriptions for SABA and other treatments • Those using BFC were prescribed a lower dose on average 	<p>Real-world data with clinical information with a large sample size</p> <p>Assessment of dosing is crude due to lack of information on dosing interval</p> <p>Little information on actual disease severity</p> <p>Industry-funded</p>

Study Author	Study Design	Population	Comparison	Outcomes	Key Findings	Strengths/Limitations
Terzano et al. ¹²	Cohort study	Italy 301 BFC (extra fine) 145 BFC 123 FSC	BFC vs. FSC	Asthma Control (controlled, partial, and uncontrolled) Healthcare utilization (outpatient and hospitalization) Mean ICS dose Quality of Life (EQ-5D)	<ul style="list-style-type: none"> • Beclomethasone (not available in Canada) was found to have better quality of life and improved asthma control • BFC users (both formulation) used lower equivalent doses of ICS 	<p>Real-world data with clinical data on variables such as FEV and smoking</p> <p>12 month follow up</p> <p>The data only comes from patients who are receiving treatment from a specialist</p>
Ye et al. ¹⁴	Cohort Study	USA 993 BFC 23, 238 FSC	BFC vs. FSC	Appropriate Use	<ul style="list-style-type: none"> • 37.5% of patients met 1 or more criteria for appropriate use • BFC users were more likely to be used appropriately compared to FSC users • Users treated by specialists were more likely to have appropriate use 	<p>Real-world data with a large sample size</p> <p>Asthma diagnosis and severity is difficult to validate</p> <p>No clinical data to validate the appropriateness of use based on disease severity</p> <p>Industry-funded</p>

Appendix B: Medline Search Strategy

1. fluticasone.mp. (3178)
2. salmeterol.mp. (2326)
3. advair.mp. (39)
4. formoterol.mp. (1652)
5. budesonide.mp. or exp Budesonide/ (4484)
6. symbicort.mp. (136)
7. formoterol.mp. (1652)
8. mometasone.mp. (672)
9. zenhale.mp. (1)
10. Dulera.mp. (4)
11. (1 and 2) or 3 (914)
12. (4 and 5) or 6 (580)
13. (7 and 8) or 9 or 10 (32)
14. (combination inhaled corticosteroid and long-acting beta agonist).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (11)
15. 11 and 12 (178)
16. 11 and 13 (6)
17. 12 and 13 (3)
18. 14 or 15 or 16 or 17 (191)
19. limit 18 to english language (177)

Appendix C: Public Plan Listings for ICS+LABA Combination Products in Canada, by Province

	Advair		Symbicort		Zenhale	BreoEllipta
	Asthma	COPD	Asthma	COPD	Asthma	COPD
BC	Res	Res	Res	No	Res	No
Alberta	Ben	Ben	Ben	Ben	No	No
Saskatchewan	Res	Res	Res	Res	Res	No
Manitoba	Ben	Ben	Ben	Ben	No	No
Ontario	Pas	No	Pas	No	Pas	No
Quebec	Res	Res	Res	Res	Res	No
New Brunswick	Res	Res	Res	Res	Res	No
Nova Scotia	Res	Res	Res	Res	Res	No
PEI	Res	Res	Res	Res	Res	No
Newfoundland	Res	Res	Res	Res	Res	No
Yukon	Res	Res	Res	Res	No	No
NIHB/NT/NU	Res	Res	Res	Res	Res	No

No=not listed

Res=restricted listing - enforced

Pas= restricting listing – passive

Ben=unrestricted listing

BC = British Columbia; NIHB = Non-Insured Health Benefits; NT = Northwest Territories; NU = Nunavut

Appendix D: Prescribed Treatment Step

Prescribed Treatment Step	Details	Drug	Daily Dose (mcg)
Step 2	Low dose ICS	Beclometason dipropionate (HFA)	100-200
	Low dose ICS	Budesonide	200-400
	Low dose ICS	Ciclesonide	80-160
	Low dose ICS	Fluticasone propionate	100-250
	Low dose ICS	Flunisolide	500-1000
	Low dose ICS	Triamcinolone acetonide	400-800
Step 3	Med/high dose ICS	Beclomethasone dipropionate (HFA)	>200-400
	Med/high dose ICS	Budesonide	>400-800
	Med/high dose ICS	Ciclesonide	>160-320
	Med/high dose ICS	Fluticasone propionate	>250-500
	Med/high dose ICS	Flunisolide	>1000-2000
	Med/high dose ICS	Triamcinolone acetonide	>800-2000
	Combination low dose ICS/LABA	Fluticasone/salmeterol (Advair diskus)	0-200
	Combination low dose ICS/LABA	Fluticasone/salmeterol (Advair HFA)	0-200
	Combination low dose ICS/LABA	Budesonide/formoterol (Symbicort DPI)	0-200
	Combination low dose ICS/LABA	Mometasone/formoterol (Zenhale)	0-200
Step 4	High dose ICS	Beclomethasone dipropionate (HFA)	>400
	High dose ICS	Budesonide	>800
	High dose ICS	Ciclesonide	>320
	High dose ICS	Fluticasone propionate	>500
	High dose ICS	Flunisolide	>2000
	High dose ICS	Triamcinolone acetonide	>2000
	Combination med/high dose ICS/LABA	Fluticasone/salmeterol (Advair diskus)	200<-<1000
	Combination med/high dose ICS/LABA	Fluticasone/salmeterol (Advair HFA)	200<-<1000
	Combination med/high dose ICS/LABA	Budesonide/formoterol (Symbicort DPI)	200<-<1600

Prescribed Treatment Step	Details	Drug	Daily Dose (mcg)
	Combination med/high dose ICS/LABA	Mometasone/formoterol (Zenhale)	200<-<800
Step 5	Combination high dose ICS/LABA	Fluticasone/salmeterol (Advair diskus)	1000+
		Fluticasone/salmeterol (Advair HFA)	1000+
		Budesonide/formoterol (Symbicort DPI)	1600+
		Mometasone/formoterol (Zenhale)	800+

Note: The GINA guidelines recommend that patients with persistent symptoms and/or exacerbations despite low dose ICS, consider step up treatment after checking for problems (inhaler technique, adherence, persistent allergen exposure and comorbidities). For adults and adolescents, the preferred step-up treatment is combination ICS/LABA.

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