ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

FINAL REPORT

ICS+LABA Combination Products for the Treatment of COPD

Pharmacoepidemiology Unit: Censored Final Report

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 Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).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

ICS+LABA combination products are the second most commonly prescribed COPD therapies 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 (all indications)

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 (9%; N=38,667) through cash payments and Non-Insured Health Benefits (NIHB). ICS+LABA combination products are commonly prescribed to patients with COPD; in fiscal 2012, 62.6% of all patients prescribed combination products had a diagnosis of COPD (with or without a concurrent asthma diagnosis). Despite being listed on the Ontario public drug formulary for the treatment of asthma only, 47.4% of all users of ICS+LABA combination products (2012) did not have any indication of such a diagnosis in administrative claims data (27.7% COPD diagnosis only [$37.2 million], 19.7% no evidence of asthma or COPD [$13.7 million]). Of the users with no evidence of asthma or COPD, 7.4% had a history of a prior respiratory disease.

Patterns of Use and Discontinuation in COPD - Ontario

In 2012, 120,990 COPD patients received provincially-funded ICS+LABA combination products in Ontario, almost one-quarter (29,151; 24.1%) of whom were new users. COPD patients prescribed ICS+LABA combination products through the OPDP were typically over 65 years of age (N=99,058; 81.9%), had moderate COPD severity (N=74,253; 61.4%), and lived in urban locations (N=102,179; 84.5%). Over half of all treated COPD patients had a concurrent diagnosis of asthma (55.7%). Advair Diskus was the most commonly prescribed combination product (44.6%), followed by Symbicort (31.8%), Advair HFA (22.4%), and Zenhale (1.2%). The majority of COPD patients who initiated both ICS and LABA between 2008 and 2013 used ICS+LABA combination products; only 2% were treated instead with concurrent single-agent ICS and LABA products ("dual therapy"). Compared to those treated with dual therapy, those treated with combination products were more adherent to therapy ($p<0.001$). Analyses adjusted for important confounders (such as history of asthma and COPD severity) found a small but significant difference in adherence to therapy between all 3 ICS+LABA combination products, with adherence being greatest among new users of Advair.

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List of Exhibits

Acknowledgments

This review was funded by grants from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Health System Research Fund and Drug Innovation Fund. The work was supported by the Institute for Clinical Evaluative Sciences (ICES), a non-profit research institute sponsored by the Ontario MOHLTC, and by the Canadian Institute for Health Information (CIHI). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES, CIHI, or the Ontario MOHLTC is intended or should be inferred.

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 COPD patients with provincial drug coverage. Specifically, this report aims to:

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

Data Sources

IMS Compuscript

IMS Compuscript provides sales data for outpatient prescriptions dispensed at retail pharmacies across Canada. Data is obtained from a representative sample of 65% of all Canadian pharmacies and is projected monthly by province. Projections incorporate the number of pharmacies in a given area, the distance between IMS-captured and uncaptured pharmacies, and the size of the uncaptured pharmacy. Projections are representative of provincial and national sales volumes. Data available through IMS Compuscript 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 Compuscript is available from the fourth quarter of 2009 to the fourth 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.(Levy et al. 67-71) 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. (Gershon et al. 388-94)

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.(Gershon et al. 183-88)

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 Compuscript to examine overall trends in the prescribing volumes of therapies use to treat COPD, 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), and short-acting anti-muscarinic agents (SAMA) dispensed between October 2009 and December 2013. Note that in these analyses, we were unable to restrict prescription volumes specifically to those patients with COPD, 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 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, and SAMA) as well as the number of users of publically-funded combination products across all indications. We also looked at demographic characteristics of patients prescribed ICS+LABA combination products for the treatment of COPD.

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. Public drug coverage is universal for individuals aged over 65, and we do not have complete eligibility information for younger beneficiaries. Therefore, we restricted this analysis to individuals aged 66 and older in order to ensure complete medication records and accurate ascertainment of new use of ICS+LABA combination therapy. 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.(Dhalla et al. 447-55;Gomes et al. E121-E127)

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.

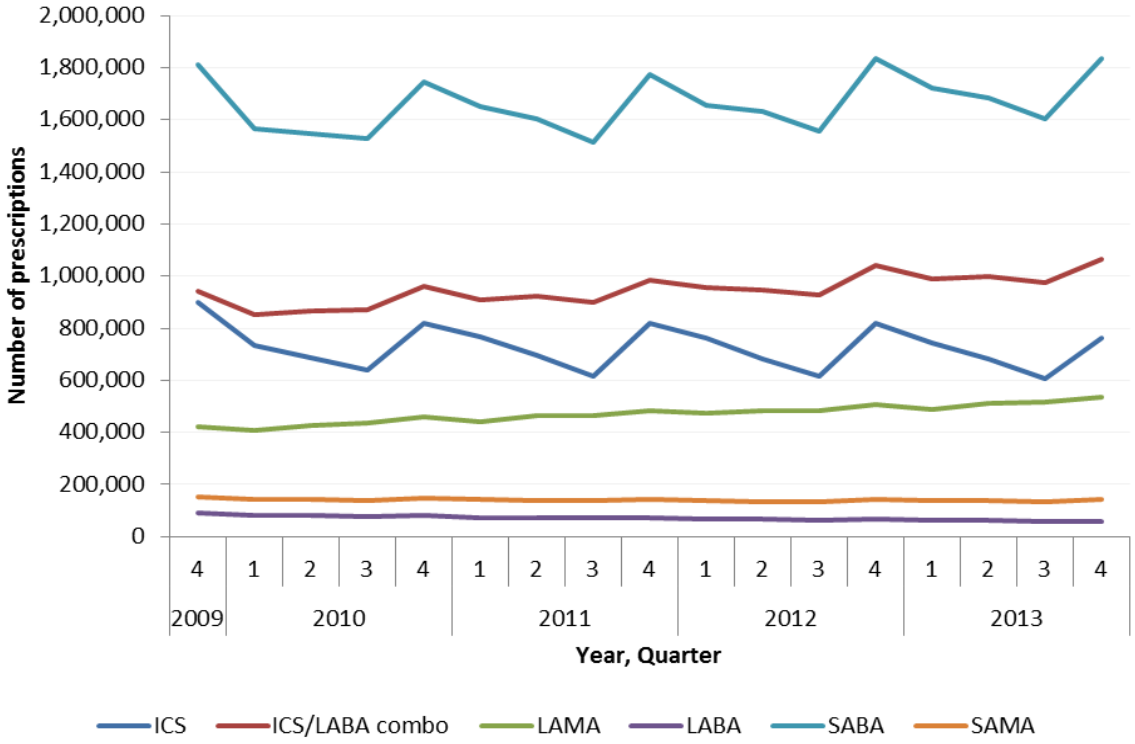
4. Breo **Ellipta** (fluticasone and vilanterol) is available in a DPI formulation. It was introduced onto the Canadian market in November 2013 and is only indicated for COPD.

Advair, Symbicort and Zenhale are listed on the Ontario public drug formulary for the treatment of asthma. Breo Ellipta is not listed on the Ontario public drug formulary and therefore 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

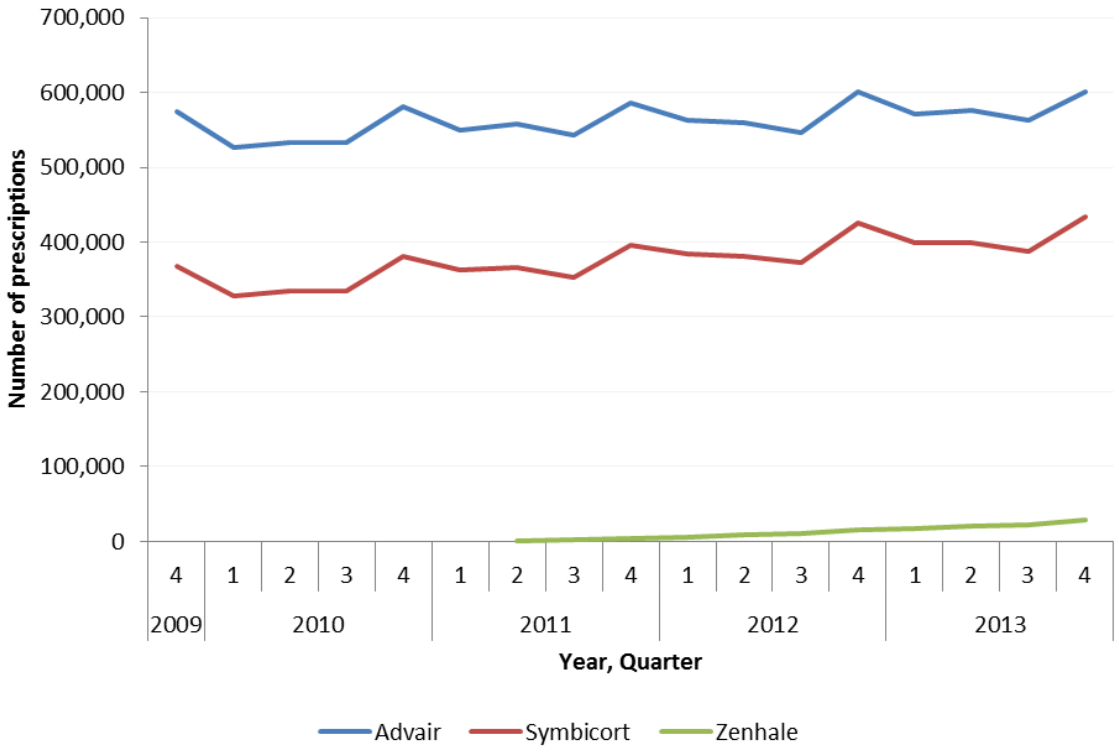


ICS+LABA combination products are the second most commonly prescribed anti-inflammatory/ bronchodilator agents in Canada.

Summary of Findings for Exhibit 1

1. Short-acting beta-agonists (SABA) are the most commonly prescribed inhaled anti-inflammatory / bronchodilator agents in Canada.
2. The prescription market share in the fourth quarter (Q4) of 2013 was:
    a. SABA products: 41.7%; 1.8 million prescriptions
    b. Inhaled corticosteroid/long-acting beta-agonist (ICS+LABA) combination products: 24.2%; 1.1 million prescriptions
    c. Inhaled corticosteroids (ICS): 17.3%; 761,746 prescriptions
    d. Long-acting anti-muscarinic agents (LAMA): 12.2%; 536,148 prescriptions
    e. Short-acting anti-muscarinic agents (SAMA): 3.2%; 140,942 prescriptions
    f. Long-acting beta-agonists (LABA): 1.4%; 60,283 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 prescribed combination product (2,309,631 prescriptions in 2013).

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

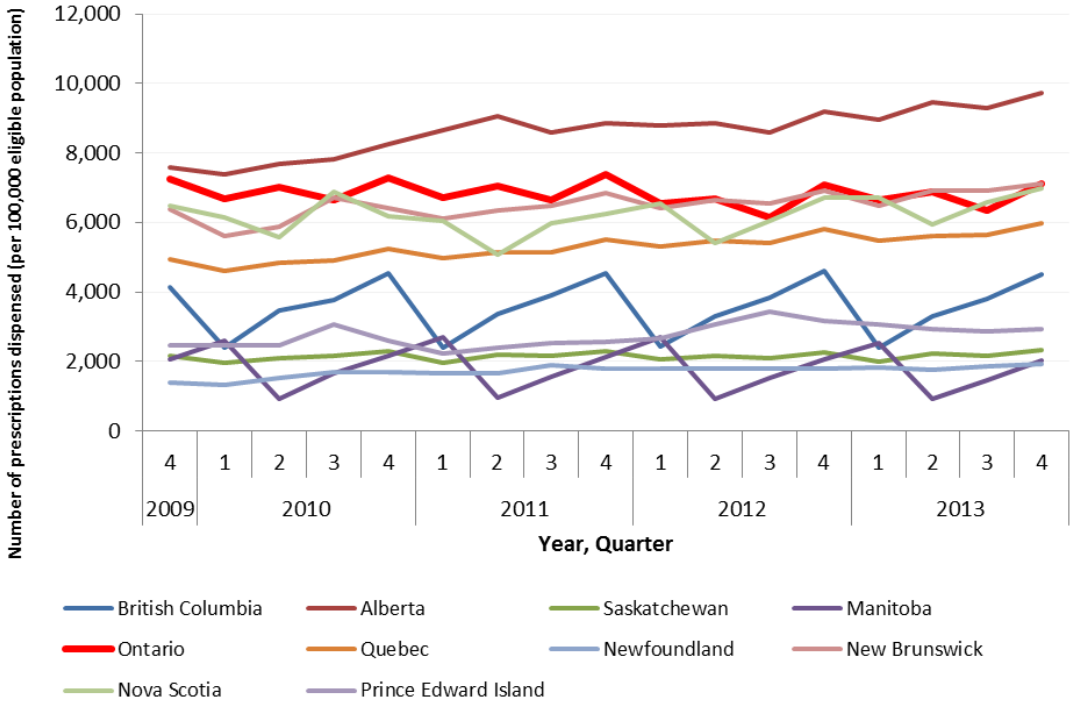
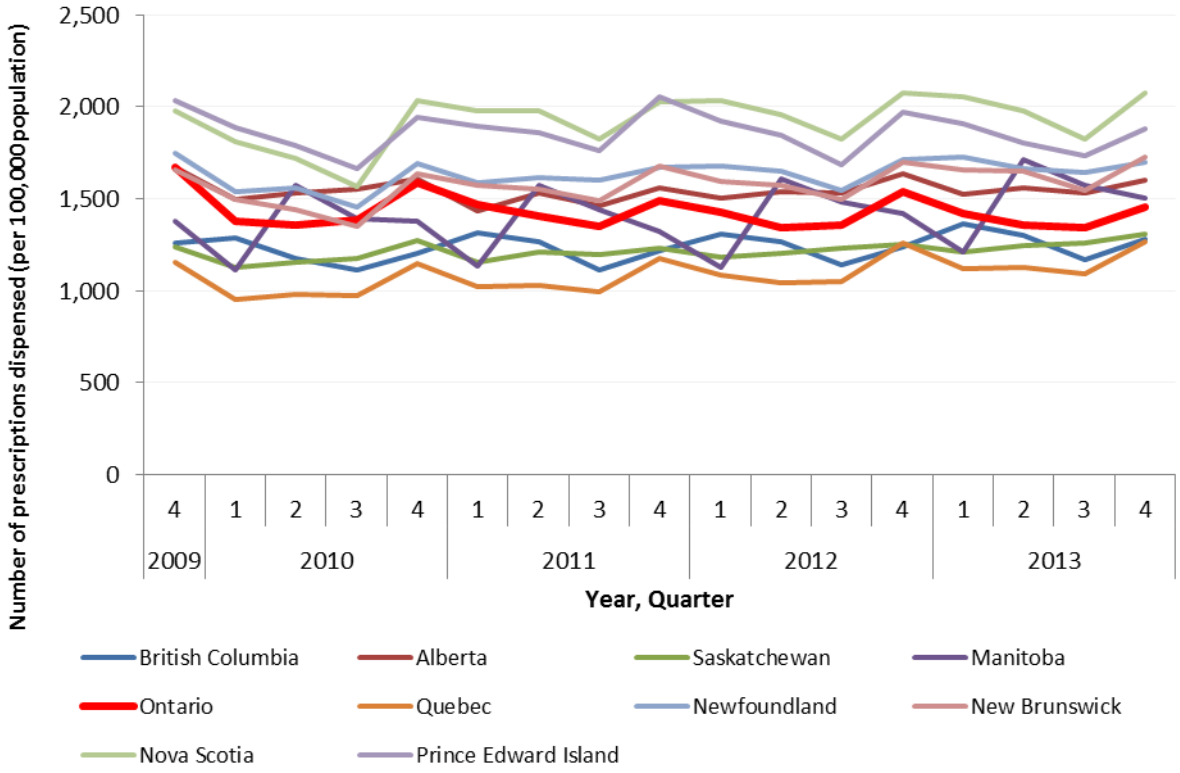


Exhibit 4: Population-adjusted utilization of non-provincially funded ICS+LABA combination products in Canada, by province



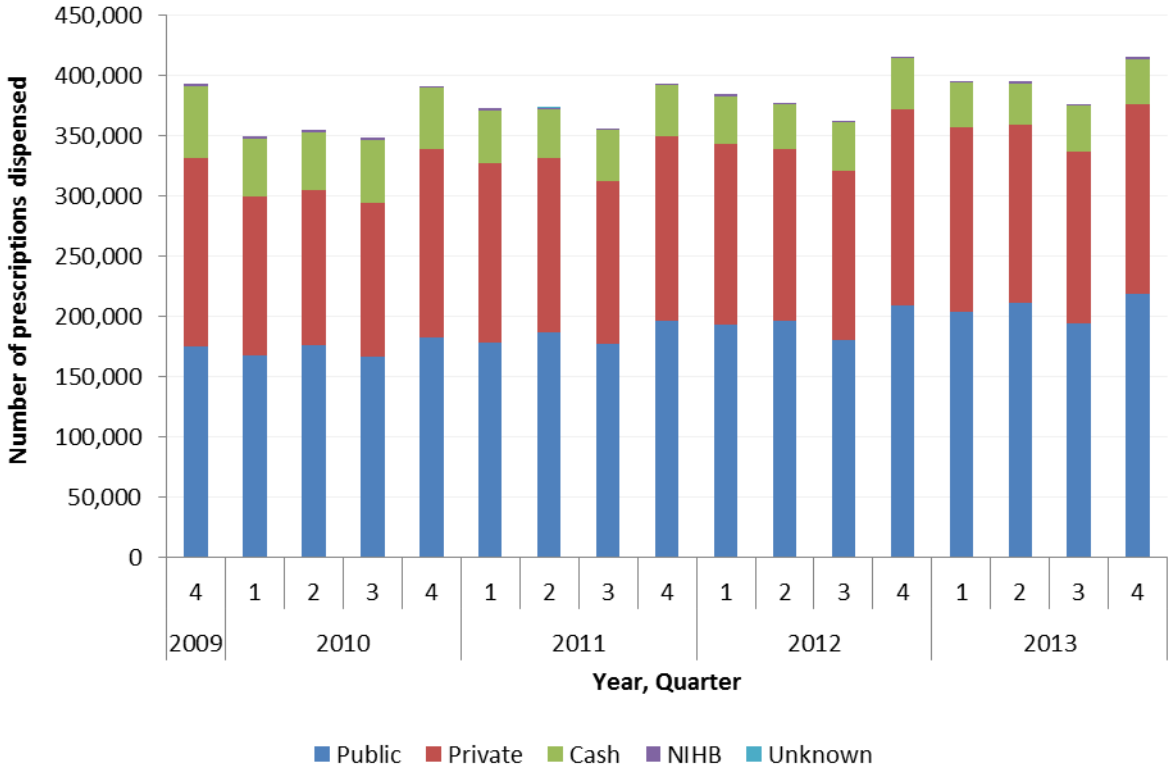
Ontario has the second highest utilization of provincially funded ICS+LABA combination products in Canada.

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. listing as general benefit on the provincial formulary).
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).
4. Non-provincially funded ICS+LABA use was on par with the national average in Ontario (1,453 prescriptions per 100,000 eligible population; national average of 1,580 prescriptions per 100,000 eligible population).

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

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

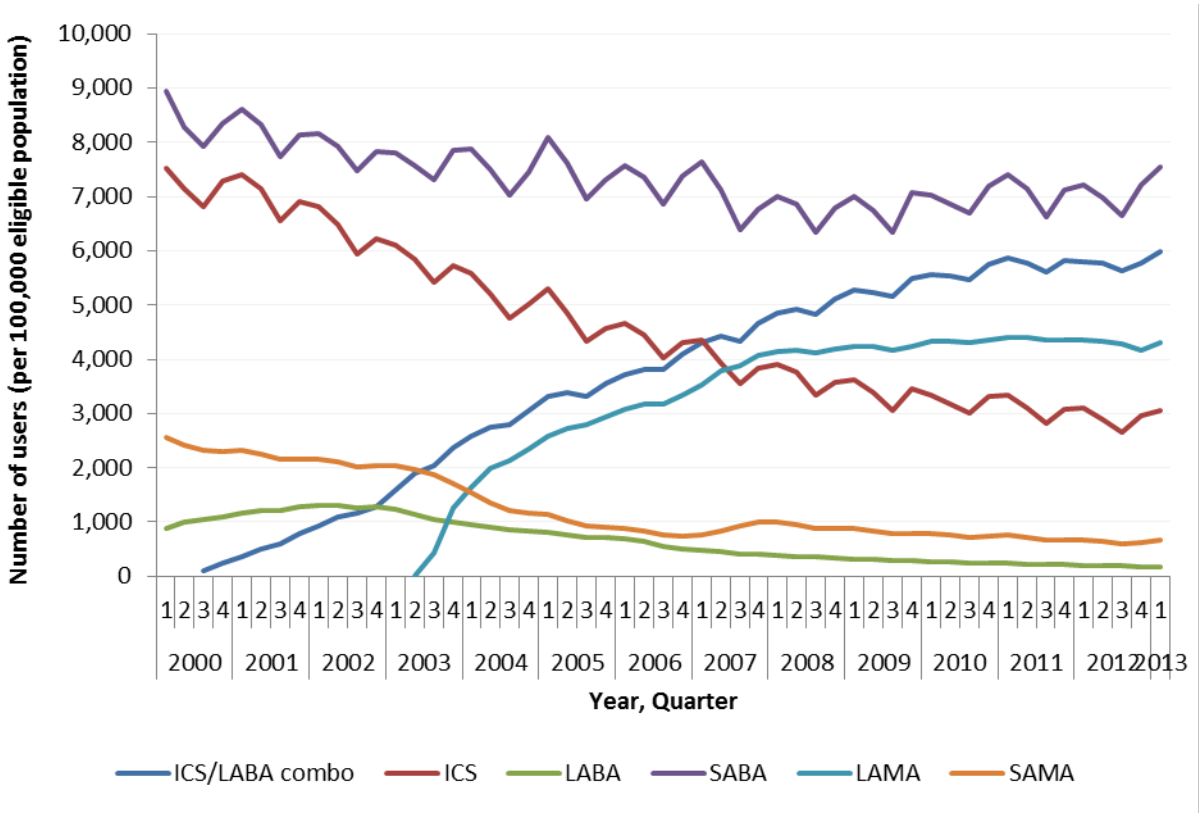


53% of ICS+LABA combination products were paid for by the Ontario Public Drug Program in the last quarter of 2013. More than 85% of ICS+LABA combination products have been paid for by private or provincially-funded drug coverage in Ontario since Q4 2009.

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: Rate of use of inhaled respiratory medications among public drug plan beneficiaries in Ontario

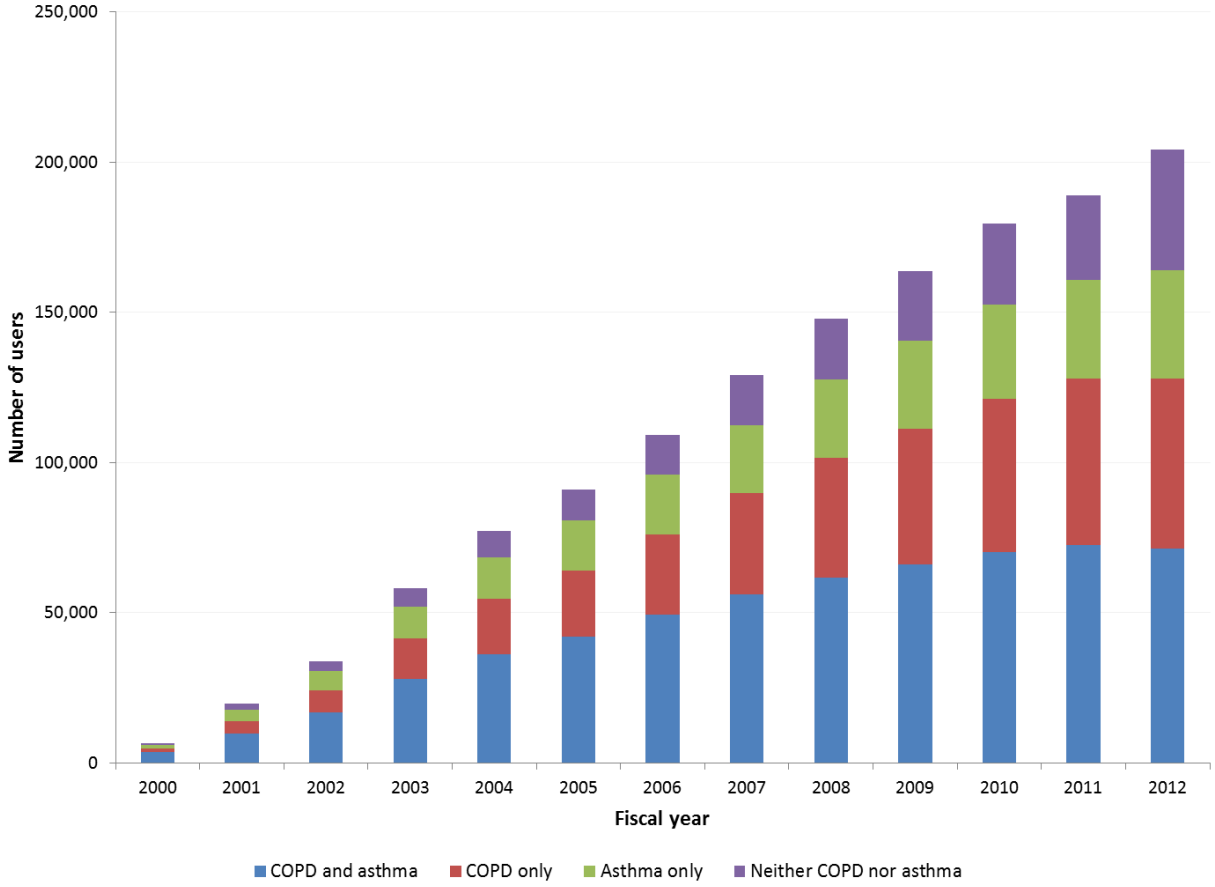


The rate of use of ICS+LABA combination products and long-acting anti-muscarinic agents (LAMAs) has increased over time, while use of all other inhaled respiratory medications has declined..

Summary of Findings for Exhibit 6

1. The rate of use of ICS+LABA combination products in Ontario increased from 111 per 100,000 beneficiaries in Q3 2000 to 5,993 per 100,000 beneficiaries in Q1 2013.
2. There was a corresponding decline in utilization of single-agent ICS and LABA products. ICS use dropped from 7,515 per 100,000 beneficiaries (Q1 2000) to 3,044 per 100,000 beneficiaries (Q1 2013), and use of LABAs declined from 881 per 100,000 beneficiaries (Q1 2000) to 178 per 100,000 beneficiaries (Q1 2013).
3. Use of long-acting anti-muscarinic agents increased markedly following their listing on the Ontario public drug formulary in 2003, reaching 4,303 per 100,000 beneficiaries in Q1 2013. Despite the steep uptake, LAMA use has plateaued in Ontario since the last quarter of 2007.

Exhibit 7: Number of users of provincially-funded ICS+LABA combination products in Ontario, by indication

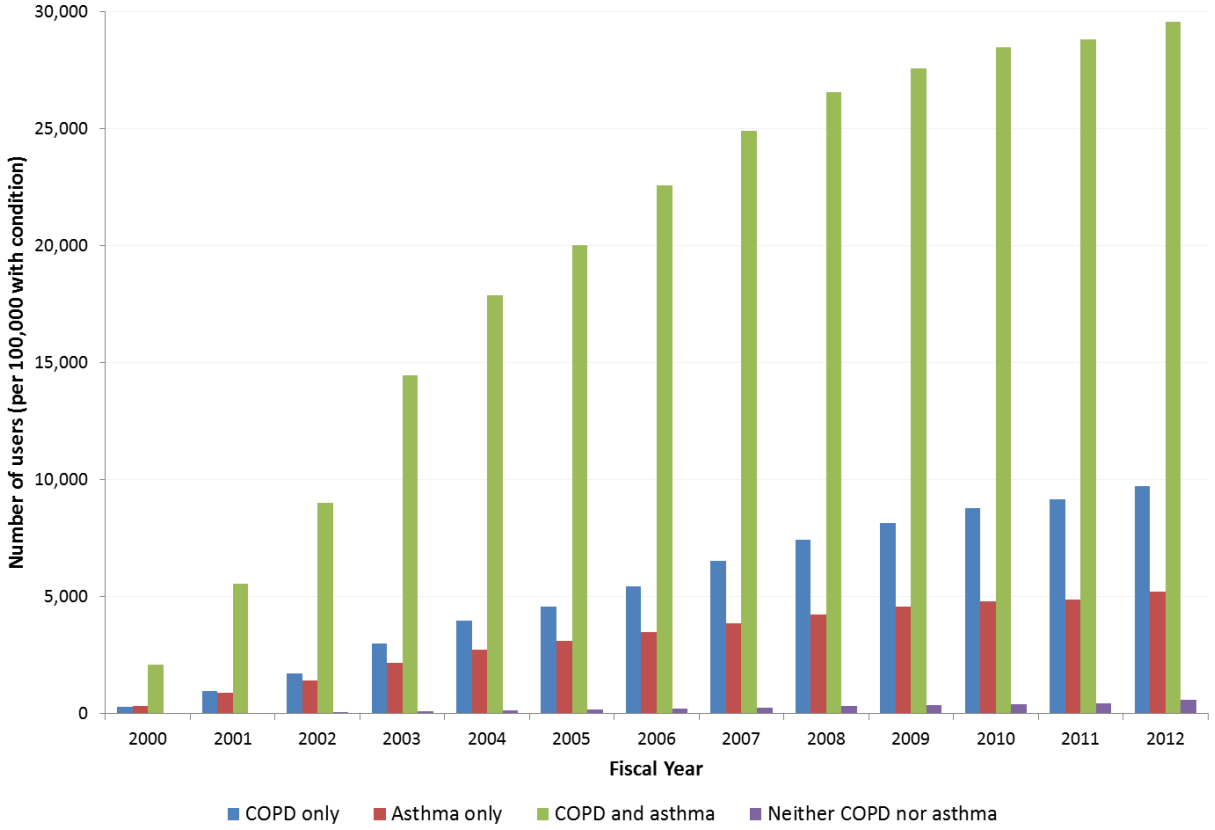


The majority (62.7%) of ICS+LABA combination products are used by individuals with COPD (either COPD alone, or concurrent COPD and asthma)

Summary of Findings for Exhibit 7

1. Use of ICS+LABA combination products among patients with only COPD (i.e. without a concurrent diagnosis of asthma) has increased nearly 50-fold, from 1,181 users in 2000 to 56,508 users in 2012.
2. Although the absolute number of users with both COPD and asthma has increased over time, the proportion of all combination therapy users with both COPD and asthma has decreased from 52.3% in 2000 to 35.0% in 2012.
3. In fiscal year 2012, 71,408 (35.0%) patients with both COPD and asthma, 56,508 (27.7%) patients with only COPD, 36,145 (17.7%) patients with only asthma, and 40,324 (19.7%) patients with no indication of COPD or asthma used ICS+LABA combination products. Of the users with no evidence of asthma or COPD, 7.4% had a history of a prior respiratory disease.

Exhibit 8: Utilization rates of provincially-funded ICS+LABA combination products among public drug plan beneficiaries in Ontario, by indication

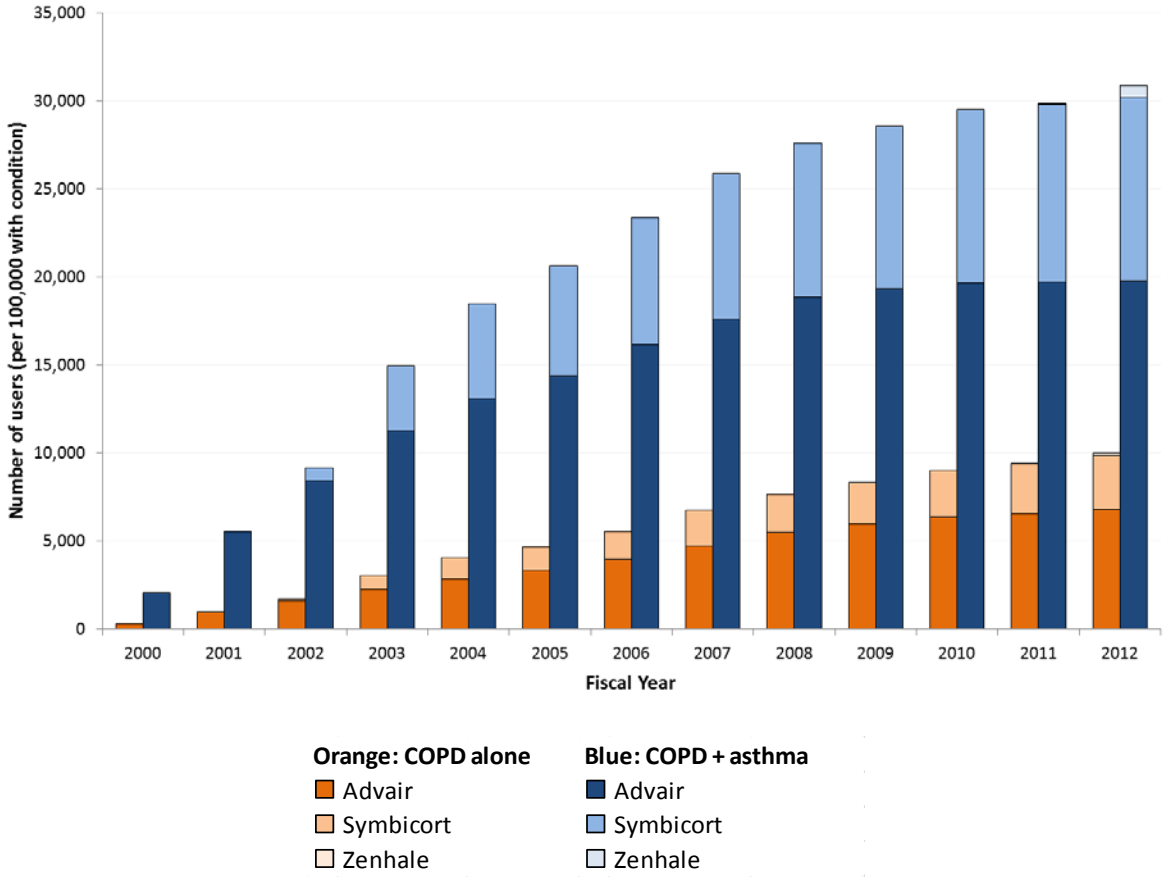


Utilization rates of ICS+LABA combination products are markedly higher among public drug plan beneficiaries with both COPD and asthma than those with other indications. Use of combination products has been increasing over time among all indications.

Summary of Findings for Exhibit 8

1. Utilization of combination products is highest among patients with both COPD and asthma, and rates have increased from 2,094 users per 100,000 patients with COPD and asthma (2000) to 29,570 users per 100,000 patients with COPD and asthma (2012).
2. Despite not being listed for the treatment of COPD on Ontario's public drug formulary, utilization rates of ICS+LABA combination products are second-highest among patients with COPD only (i.e. among COPD patients without a concurrent diagnosis of asthma). Rates among this group have increased 32-fold, from 295 per 100,000 patients (2000) to 9,724 per 100,000 patients (2012).
3. Similarly, among patients with asthma only, rates of use of combination products have increased 15-fold, from 333 per 100,000 patients (2000) to 5,197 per 100,000 patients (2012).
4. Utilization rates were lowest among individuals with no indication of COPD or asthma, but have still increased considerably over the past 13 years (from 11 per 100,000 patients [2000] to 593 per 100,000 patients [2012]).

Exhibit 9: Utilization rates of provincially-funded ICS+LABA combination products among patients with COPD, by asthma status and product

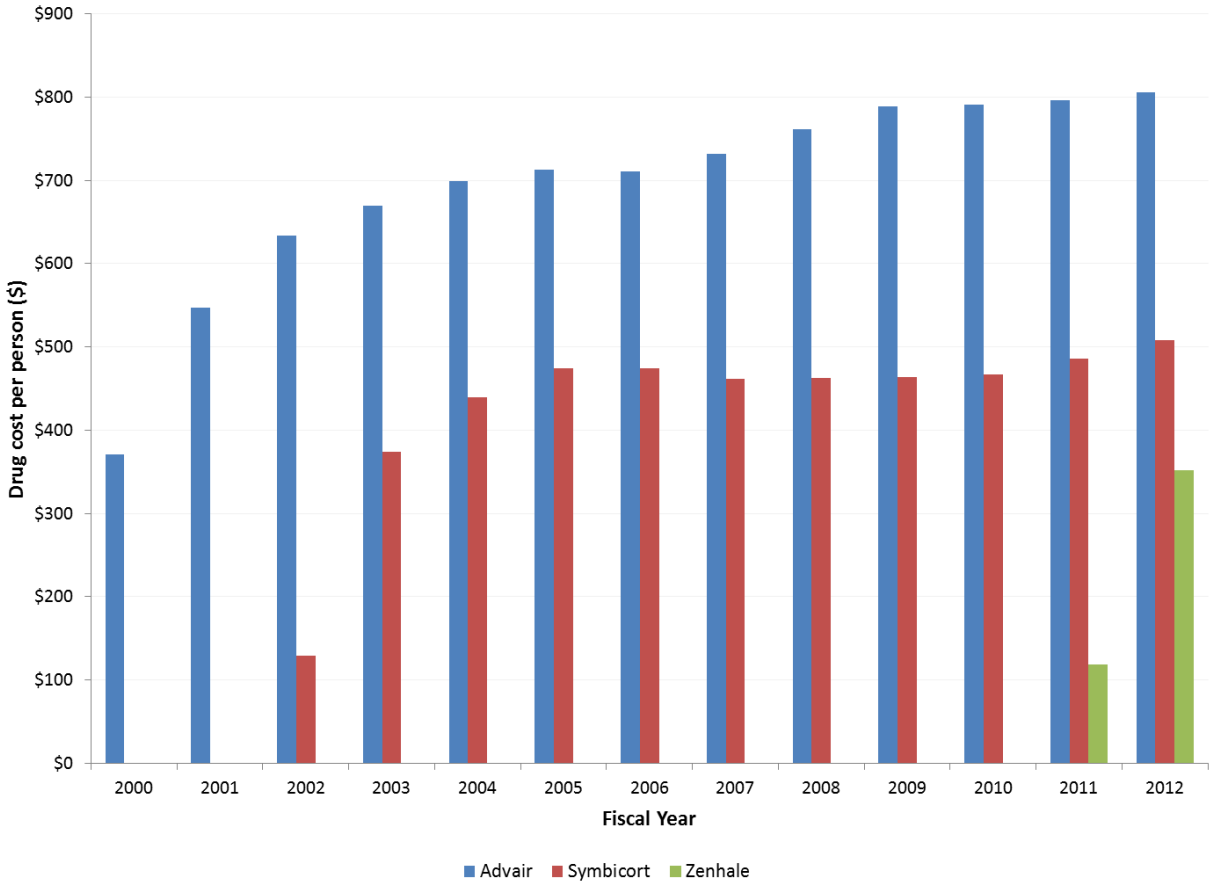


Advair had the highest utilization rates, regardless of indication. Utilization of ICS+LABA combination products was markedly higher among COPD patients with asthma.

Summary of Findings for Exhibit 9

1. Rates of Advair use have increased among COPD patients, from 820 users per 100,000 patients in fiscal 2000 to 10,604 per 100,000 patients in 2012. Similarly, use of Symbicort has increased from 293 per 100,000 COPD patients to 5,201 per 100,000 COPD patients.
2. In general, use of Advair is markedly higher than Symbicort. In 2012, there were almost twice as many Advair users than Symbicort among patients with COPD alone (N=39,547 vs. 17,613), and more than twice as many Advair users among patients with concurrent asthma diagnoses (N=25,174 vs. 47,685).
3. Zenhale was added to the Ontario public drug formulary in February 2012 and is only indicated for use in asthma. As a result, the rate of use of Zenhale among patients with both COPD and asthma was higher than that among those with COPD alone (689 per 100,000 vs. 190 per 100,000 patients in 2012).

Exhibit 10: Per-person cost of ICS+LABA combination products among patients with COPD, by product



The average annual cost per person for ICS+LABA combination therapy was highest among Advair users, followed by Symbicort and Zenhale.

Summary of Findings for Exhibit 10

1. In fiscal 2012, the average annual cost per-person of ICS+LABA combination therapy among patients with COPD (either with or without concurrent diagnoses of asthma) was $806 for Advair users, $508 for Symbicort users, and $352 for Zenhale users.
2. The average cost of Advair has almost doubled since fiscal year 2001 (the first full year of Advair availability), from $547 per person to $806 per person.
3. The average cost of Symbicort has increased 35.8% since fiscal 2003 (the first full year of Symbicort availability), from $374 per person to $508 per person.

Methodological Note

Fiscal year 2012 was the first full year in which Zenhale was available. Average annual costs in 2012 were $352 per person.

Characteristics of users of provincially-funded ICS+LABA combination products in Ontario

Exhibit 11: Baseline characteristics of COPD patients treated with provincially-funded ICS+LABA combination products in Ontario, by age, Fiscal Year 2012/13

	OVERALL	AGE < 65	AGE 65+
Number of COPD patients treated	120,990	21,932	99,058
Number of new ICS+LABA users	29,151 (24.1%)	6,120 (27.9%)	23,031 (23.3%)
Age (Median, IQR)	74.4 (67.9-81.4)	56.4 (51.1-61.0)	76.9 (71.4-82.8)
Males	55,461 (45.8%)	9,190 (41.9%)	46,271 (46.7%)
LTC resident	6,515 (5.4%)	411 (1.9%)	6,104 (6.2%)
Urban residence	102,179 (84.5%)	18,534 (84.5%)	83,645 (84.4%)
Socioeconomic status			
Missing	500 (0.4%)	133 (0.6%)	367 (0.4%)
Q1 (lowest)	31,944 (26.4%)	9,487 (43.3%)	22,457 (22. 7%)
Q2	26,728 (22.1%)	4,995 (22.8%)	21,733 (21.9%)
Q3	22,864 (18.9%)	3,252 (14.8%)	19,612 (19.8%)
Q4	20,713 (17.1%)	2,423 (11.1%)	18,290 (18.5%)
Q5 (highest)	18,241 (15.1%)	1,642 (7.5%)	16,599 (16.8%)
History of asthma	67,431 (55.7%)	13,804 (62.9%)	53,627 (54.1%)
COPD severity			
Moderate	74,253 (61.4%)	13,771 (62.8%)	60,482 (61.1%)
Severe	22,130 (18.3%)	4,707 (21.5%)	17,423 (17.6%)
Very severe	24,607 (20.3%)	3,454 (15.8%)	21,153 (21.4%)
COPD maintenance therapy (previous 1 year)	93,693 (77.4%)	17,923 (81.7%)	75,770 (76.5%)
ICS	13,495 (11.2%)	3,187 (14.5%)	10,308 (10.4%)
LABA	1,489 (1.2%)	218 (1.0%)	1,271 (1.3%)
LAMA	62,193 (51.4%)	10,155 (46.3%)	52,038 (52.5%)
SABA	73,678 (60.9%)	15,860 (72.3%)	57,818 (58.4%)
SAMA	9,439 (7.80%)	1,805 (8.23%)	7,634 (7.71%)
Theophylline	3,619 (3.0%)	595 (2.7%)	3,024 (3.1%)
Treatment for COPD exacerbations (previous 1 year)[1]	60,839 (50.3%)	11,006 (50.2%)	49,833 (50.3%)
Number of puffs dispensed, per user (Median, IQR)[2]	600 (240-960)	600 (240-1,080)	600 (240-960)
Number of puffers dispensed, per user (Median, IQR)[2]	6 (3-12)	6 (3-12)	6 (3-12)
Cost of prescriptions, per user (Mean, SD)[2]	$734 ($540)	$726 ($576)	$736 ($531)

[1] Defined as any prescription for an oral, short-duration antibiotic or oral steroid
[2] Over fiscal year 2012/13

There were 120,990 COPD patients who were treated with provincially-funded ICS+LABA combination products in fiscal 2012, almost one-quarter (24.1%) of whom were new users. These patients tended to be older, have moderate COPD severity, and live in urban areas.

Summary of Findings for Exhibit 11

1. There were 120,990 COPD patients treated with provincially-funded ICS+LABA combination products in fiscal 2012, 29,151 (24.1%) of whom were new ICS+LABA users.
2. The majority of treated COPD patients were over 65 years of age (N=99,058, 81.9%), had moderate COPD severity (N=74,253, 61.4%), lived in urban areas (N=102,179, 84.5%), were not living in long term care facilities (N=114,475, 94.6%) and had lower socioeconomic status
3. Older users had more advanced disease (21.4% of those aged 65 and over had very severe COPD, compared to 15.8% among users aged under 65), but were less likely to have been prescribed other COPD therapy prior to initiating ICS+LABA combination therapy (76.5% vs. 81.7% among younger users).
4. The majority of ICS+LABA combination product use was among individuals with moderate COPD severity (61.4%). Only 1 in 5 users of these products had very severe COPD (N=24,607; 20.3%).
5. Half of all COPD patients using ICS+LABA products were treated for a COPD exacerbation in the previous year (N=60,839, 50.3%).
6. Concurrent diagnosis with asthma was more common among those aged under 65 (62.9%; N=13,804) compared to those aged 65 and older (54.1%; N=53,627).

Exhibit 12: Baseline characteristics of COPD patients 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 (%)
Number of COPD patients treated	120,990	53,932	27,100	38,481	1,477
Number of new ICS+LABA users	29,151 (24.1%)	11,384 (21.1%)	6,677 (24.6%)	10,041 (26.1%)	1,049 (71.0%)
Age (Median, IQR)	74.4 (67.9-81.4)	74.7 (68.1-81.5)	75.1 (67.9-82.4)	73.7 (67.7-80.5)	73.0 (66.7-79.5)
Males	55,461 (45.8%)	25,533 (47.3%)	11,907 (43.9%)	17,383 (45.2%)	638 (43.2%)
LTC resident	6,515 (5.4%)	2,753 (5.1%)	2,600 (9.6%)	1,144 (3.0%)	18 (1.2%)
Urban residence	102,179 (84.5%)	45,858 (85.0%)	23,114 (85.3%)	31,880 (82.9%)	1,327 (89.8%)
Socioeconomic status					
Missing	500 (0.4%)	212 (0.4%)	124 (0.5%)	158 (0.4%)	6 (0.4%)
Q1 (lowest)	31,944 (26.4%)	14,217 (26.4%)	7,595 (28.0%)	9,726 (25.3%)	406 (27.5%)
Q2	26,728 (22.1%)	11,966 (22.2%)	6,113 (22.6%)	8,341 (21.7%)	308 (20.9%)
Q3	22,864 (18.9%)	10,101 (18.7%)	5,167 (19.1%)	7,337 (19.1%)	259 (17.5%)
Q4	20,713 (17.1%)	9,342 (17.3%)	4,366 (16.1%)	6,750 (17.5%)	255 (17.3%)
Q5 (highest)	18,241 (15.1%)	8,094 (15.0%)	3,735 (13.8%)	6,169 (16.0%)	243 (16.5%)
History of asthma	67,431 (55.7%)	29,384 (54.5%)	14,718 (54.3%)	22,538 (58.6%)	791 (53.6%)
COPD severity					
Moderate	74,253 (61.4%)	32,074 (59.5%)	15,565 (57.4%)	25,694 (66.8%)	920 (62.3%)
Severe	22,130 (18.3%)	9,683 (18.0%)	4,995 (18.4%)	7,109 (18.5%)	343 (23.2%)
Very severe	24,607 (20.3%)	12,175 (22.6%)	6,540 (24.1%)	5,678 (14.8%)	214 (14.5%)

	Overall N (%)	Advair Diskus N (%)	Advair HFA[1] N (%)	Symbicort N (%)	Zenhale[2] N (%)
COPD maintenance therapy (previous 1 year)	93,693 (77.4%)	43,419 (80.5%)	22,288 (82.2%)	26,905 (69.9%)	1,081 (73.2%)
ICS	13,495 (11.2%)	5,291 (9.8%)	3,806 (14.0%)	3,963 (10.3%)	435 (29.5%)
LABA	1,489 (1.2%)	670 (1.2%)	263 (1.0%)	487 (1.3%)	69 (4.7%)
LAMA	62,193 (51.4%)	30,863 (57.2%)	14,088 (52.0%)	16,699 (43.4%)	543 (36.8%)
SABA	73,678 (60.9%)	33,845 (62.8%)	18,680 (68.9%)	20,276 (52.7%)	877 (59.4%)
SAMA	9,439 (7.80%)	4,141 (7.68%)	2,957 (10.91%)	2,242 (5.83%)	99 (6.70%)
Theophylline	3,619 (3.0%)	1,881 (3.5%)	716 (2.64)	988 (2.6%)	34 (2.3%)
Treatment for COPD exacerbations (previous 1 year)[3]	60,839 (50.3%)	27,379 (50.8%)	14,208 (52.4%)	18,439 (47.9%)	813 (55.0%)
Number of puffs dispensed, per user (Median, IQR)[4]	600 (240-960)	600 (240-840)	600 (240-1,080)	600 (240-1,080)	240 (120-600)
Number of puffers dispensed, per user (Median, IQR)[4]	6 (3-12)	10 (4-14)	5 (2-9)	5 (2-9)	2 (1-5)
Cost of prescriptions, per user (Mean, SD)[4]	$734 ($540)	$851 ($568)	$787 ($556)	$546 ($424)	$386 ($383)

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

[2] Zenhale added to the provincial drug formulary in February 2012

[3] Defined as any prescription for an oral, short-duration antibiotic or oral steroid

[4] Over fiscal year 2012/13

Among the 120,990 COPD patients treated with ICS+LABA combination products in fiscal year 2012, Advair Diskus was the most commonly used product, followed by Symbicort, Advair HFA and Zenhale.

Summary of Findings for Exhibit 12

1. Among the 120,990 COPD patients treated with an ICS+LABA combination product in fiscal 2012, 44.6% (N=53,932) were prescribed Advair Diskus, 31.8% (N=38,481) were prescribed Symbicort, 22.4% (N=27,100) were prescribed Advair HFA and 1.2% (N=1,477) were prescribed Zenhale.
2. Advair users were more likely to be residents of long-term care facilities (5.1% among Advair Diskus users and 9.6% among Advair HFA users vs. 3.0% among Symbicort users and 1.2% among Zenhale users) and have previous use of other COPD therapies (80.5% among Advair Diskus users and 82.2% among Advair HFA users vs. 69.9% among Symbicort users and 73.2% among Zenhale users).
3. COPD patients prescribed Advair (Diskus or HFA) were more likely to have very severe COPD (22.6% and 24.1%, respectively) compared to Symbicort (14.8%) and Zenhale (14.5%).
4. In 2012, the median number of puffers dispensed per user was highest for Advair Diskus (median of 10), followed by Advair HFA and Symbicort (median 5 puffers), and lowest for Zenhale (median 2 puffers). However, the median number of puffs dispensed per user was the same for Advair Diskus, Advair HFA and Symbicort (median 600 puffs), and lower for Zenhale (median 240 puffs).
5. The mean cost per user of prescriptions used over the fiscal year was highest for Advair Diskus ($851), followed by Advair HFA ($787) and Symbicort ($546), and lowest for Zenhale ($386).

Methodological Note

Zenhale was added to the formulary in February 2012. The lower numbers of puffers, puffs, and costs are likely influenced by patients only using these products for part of the year.

Patterns of COPD therapy use and discontinuation

Exhibit 13: Time to discontinuation among new users of ICS+LABA products

ICS+LABA	Received Only 1 Prescription %	Median time to discontinuation*
ICS+LABA Combination Therapy	30-40%	9-12 months
Advair	30-40%	9-12 months
Symbicort	40-50%	9-12 months
Zenhale	30-40%	6-9 months
ICS + LABA Dual Therapy	0%**	6-9 months

*Among those prescribed >1 prescription

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

In general, individuals treated with combination ICS+LABA products adhere to therapy for longer than those treated with ICS + LABA dual therapy

Summary of Findings for Exhibit 13:

1. Over one-third of COPD patients initiating an ICS+LABA combination product received only one prescription before discontinuing therapy.
2. Those who continued therapy were more adherent to ICS+LABA therapy compared to those treated with dual ICS+LABA therapy ($p<0.0001$).
3. Approximately one-third of new users of Advair and Zenhale discontinued therapy after only one prescription. This was higher among those initiating Symbicort.
4. Among those patients receiving multiple prescriptions for an ICS+LABA combination product, the median time to discontinuation was similar between users of Advair and Symbicort ($p=0.55$), but different among users of Zenhale. After adjusting for important confounders (including COPD severity), time to discontinuation differed significantly between all three products (Advair users least likely to discontinue therapy).
5. Almost two-thirds of patients treated with ICS+LABA products received concomitant COPD drugs over the course of their therapy.

Methodological Note

Adherence to Zenhale was likely influenced by the short follow-up time for this drug since it was only added to the formulary in 2012.

Key Findings

National and Provincial Trends in ICS+LABA Prescribing

Inhaled corticosteroid / long-acting beta-agonist (ICS+LABA) combination products are the second-most commonly prescribed inhaled respiratory medications in Canada (second to short-acting beta-agonists), with 1.1 million prescriptions dispensed in the fourth quarter of 2013. Over half of all prescriptions for ICS+LABA combination products dispensed in Canada were for Advair. Zenhale, which was only added to the Canadian market in 2011 and is only indicated for the treatment of asthma, comprised only 3% of the market share at the end of 2013.

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 the last quarter of 2013). In contrast, use of combination products paid for by non-provincial means (i.e. private insurance, cash payments, Non-Insured Health Benefits) was on par with the national average (1,453 prescriptions per 100,000 eligible population in Ontario; national average of 1,580 prescriptions per 100,000 eligible population, 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 the last quarter of 2013, 53% of prescriptions were paid for through provincial drug coverage, 38% through private health insurance, 9% cash payments, and <1% through Non-Insured Health Benefits.

The number of users of ICS+LABA combination products has been increasing over time, whereas use of all other respiratory therapies (with the exception of long-acting anti-muscarinic agents) has declined. Use of combination therapies is highest among patients with both COPD and asthma and second-highest among patients with COPD only (i.e. without a concurrent asthma diagnosis), despite the fact that combination products are listed on the public drug formulary for treatment of asthma only. Furthermore, almost 20% of patients who received a prescription for an ICS+LABA combination product did not appear to have a diagnosis for asthma or COPD (7% of whom had a history of a prior respiratory disease).

Patterns of Use and Discontinuation

In 2012, there were 204,295 users of provincially-funded ICS+LABA combination products. Of these, 120,990 (59%) had a diagnosis of COPD, and almost one-quarter (29,151; 24.1%) were new users of combination products. In general, COPD patients receiving provincially-funded ICS+LABA combination products tended to be over 65 years of age, have moderate COPD severity, and live in urban locations. Prevalence of concurrent asthma diagnosis was higher among younger patients (<65 years of age), although more than half of all COPD patients had a concurrent diagnosis of asthma. Advair Diskus was

the most commonly prescribed combination product, followed by Symbicort, Advair HFA, and Zenhale.

Almost all (98%) COPD patients treated with combination therapy were dispensed ICS+LABA combination products; the remaining 2% were prescribed concurrent therapy with single-agent ICS and LABA products. Adherence to therapy was highest among those prescribed combination products compared to dual therapy. In general, there were no major differences in adherence between users of Advair and Symbicort, however analyses adjusted for important confounders (such as history of asthma and COPD severity) found a small but significant difference in adherence to therapy between all 3 ICS+LABA combination products.

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 COPD management.

Health Equity

Stratified analyses suggest that there isn't a major equity issue in access to these medications by age or gender. Overall, ICS+LABA combination products were slightly more common among women (approximately 54%); utilization was higher among older patients, which aligns with the higher prevalence of COPD among seniors and among females.

This analysis suggests that although public drug coverage for ICS+LABA combination products in Ontario is restricted to individuals with asthma, patients requiring these medications for treatment of COPD are still managing to access these medications as needed. In fact, at the end of 2013, almost one-third (28%) of provincially-funded combination product users had a diagnosis of COPD without concurrent asthma.

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 Compuscript 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. Diagnoses of COPD and asthma 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 picked up in the administrative data.
5. Our definition of COPD severity is limited to the information available through administrative data holdings, which does not include clinical measures such as forced expiratory volume (FEV). However, the definition was developed based on consultation with clinical experts to attempt to approximate the severity measures reported in the GOLD guidelines. It incorporates a variety of measures such as exacerbations, emergency department visits, hospitalizations, oxygen therapy and lung reduction procedures in an attempt to obtain as close an approximation to true severity as possible with the data available.

Generalizability

1. All analyses using IMS Compuscript 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 35 and older, and therefore are generalizable to only this adult population.

3. Due to incomplete data on public drug plan eligibility in Ontario among those aged less than 65 years, we restricted our analysis of drug adherence among new users of ICS+LABA combination products to patients aged 66 and older. Therefore, these findings may not be generalizable to the younger population of ICS+LABA users.

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.

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 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.

Methods

Search Strategy

We performed a Medline search for all literature published between 1996 and January 2014. Search terms included budesonide, formoterol, fluticasone, salmeterol, Advair, Symbicort, and combination inhaled corticosteroid and long-acting beta agonist. Overall, 165 abstracts were reviewed, and potentially relevant articles were obtained in full text. Four studies submitted through Evidence Submission Packages were also considered for inclusion in the review.

Inclusion Criteria:

- English Language
- Published between 1996 and January 2014
- COPD 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 6 studies were included in the final review. Five of these studies compared effectiveness, safety and/or adherence of budesonide/formoterol to fluticasone/salmeterol products. One compared fluticasone/salmeterol to dual therapy with an ICS and LABA. See Table 1 for a summary of all included studies.

Results

Budesonide/formoterol vs. fluticasone/salmeterol

We identified 5 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 COPD exacerbations, adherence, health services utilization, and pneumonia.

COPD Exacerbations

Four studies compared rates of COPD exacerbations between users of BFC vs. FSC.(Roberts et al. 769-76;Mapel et al. 60-68;Larsson et al. 584-94;Blais, Forget, and Ramachandran 1320-28) All four studies were funded by AstraZeneca (the manufacturer of the BFC product).

Two studies conducted in the United States (US) by the same group of authors found no overall difference in COPD exacerbations between the two exposure groups.(Roberts et al. 769-76;Mapel et al. 60-68) The first such study by Roberts et al. was a propensity-matched cohort study among new users of either BFC or FSC in a large database of healthcare claims for more than 55 million patients and 90 US health insurance plans between 2007 and 2009.(Roberts et al. 769-76) The mean age of patients included in this study was 61 years, and after matching (N=3,385 in each group) were similar with respect to demographic characteristics and baseline comorbid conditions. This study found no significant differences in rates of COPD exacerbation events within 6 months of treatment initiation between groups (63.4%, N=2,146 among BFC users compared to 62.5%, N=2,116 among FSC users; p=0.45). Major COPD exacerbations resulting in hospitalization were also similar between groups (4.1%, N=140 among BFC users compared to 3.5%, N=117 among FSC users; p=0.144). The use of SABAs and ipratropium were significantly lower among BFC users compared to FSC users (34.7% vs. 39.5% (p<0.001) and 9.8% vs 7.8% (p=0.005) for SABA and ipratropium, respectively). A second study by the same group of authors again investigated risks of COPD exacerbations within a 6 month follow-up among a propensity matched cohort of patients newly initiating either BFC or FSC among the same US population, over a slightly different study period (July 2006 to June 2010).(Mapel et al. 60-68) In this study, Mapel et al. report a main outcome of severe COPD exacerbations, defined as a hospitalization or ED visit with a primary respiratory diagnosis (COPD, pneumonia, or respiratory distress). Following propensity score matching (3,852 subjects in each exposure group), patients in both treatment groups had a significantly reduced number of COPD exacerbations compared to baseline. However, the authors reported no significant difference in rates of COPD-related hospitalizations (3.6% vs. 3.1% for BFC vs. FSC, respectively; p=0.23) or COPD-related ED visits (1.5% vs. 1.9% for BFC vs. FSC, respectively; p=0.21) between exposure groups over the 6 month follow-up.

Two additional studies compared ICS+LABA combination products in Sweden and Canada, and both studies concluded that users of BFC had fewer hospital encounters related to COPD exacerbations compared to FSC users. Larsson et al. conducted a propensity-matched cohort study using healthcare databases from 76 primary care centres in Sweden (covering approximately 8% of the Swedish population).(Larsson et al. 584-94) The authors matched 2,734 FSC users to an equal number of BFC users, and used Poisson models to compare the mean rate of outcomes between treatment groups over an average of 3.5 years follow-up. On average, the matched study population was 67.6 years of age, and 53% were female. The two treatment groups did not differ significantly for any measured baseline characteristics, including history of exacerbations, health services utilization, past COPD mediation use, and comorbid factors. This study found that individuals treated with BFC had fewer COPD exacerbations per patient-year compared to those treated with FSC (mean 0.80 vs. 1.09 exacerbations; Rate Ratio (RR) 0.74, 95% confidence interval (CI) 0.69 to 0.79; p<0.0001). A subgroup analysis among patients aged 60 years and older found consistent results (mean 0.80 vs 1.16 exacerbations (BFC vs. FSC); RR 0.69, 95% CI

0.65 to 0.75). A second study, conducted by Blais et al. in Quebec, Canada reported the findings of a matched cohort study comparing risks of COPD exacerbations among new users of BFC and FSC in the 1 year following treatment initiation.(Blais, Forget, and Ramachandran 1320-28) The 2,262 individuals in the matched cohort had an average age of 62 years, and 52.1% were men. Following matching, several important differences in baseline characteristics remained, including BFC users being more likely to initiate treatment from a respiratory specialist, and FSC users having a higher mean number of days in hospital prior to initiating ICS+LABA therapy. Although the authors found no significant difference in the primary outcome of any COPD exacerbation (defined as ED visit, hospitalization, or short-course prescription for oral corticosteroids) between BSC and FSC (adjusted RR 0.88, 95% CI 0.78 to 1.00), those initiating BFC were significantly less likely to have ED visits (adjusted RR 0.75, 95% CI 0.58 to 0.97) or hospitalizations (adjusted RR 0.61, 95% CI 0.47 to 0.81) for COPD.

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 in each study. Both studies conducted in the US (Mapel and Roberts) only followed patients forward for up to 6 months, and reported no significant differences in rates of COPD exacerbations, while the two studies following patients for longer (1 year and 3.5 years) reported significant differences between treatment groups, favouring BFC.(Larsson et al. 584-94;Blais, Forget, and Ramachandran 1320-28) However, the results from Blais et al. must be interpreted with care, as the matching did not appear to create treatment groups that were comparable at baseline, and therefore unmeasured confounding may have influenced these findings.(Blais, Forget, and Ramachandran 1320-28)

Pneumonia

Two studies compared the risk of pneumonia between individuals with COPD treated with BFC and FSC. In the propensity-matched cohort study by Roberts et al. described previously, the authors also compared rates of pneumonia-related health services utilization between exposure groups.(Roberts et al. 769-76) This study found no significant difference in rates of pneumonia-related hospitalizations (1.8% vs. 1.9% for BFC and FSC, respectively; p=0.65) or emergency department visits (0.2% vs. 0.2% for BFC and FSC, respectively; p=1.00) between the two treatment arms. There was a small, marginally significant difference in rates of outpatient visits related to pneumonia between the two groups, favouring the use of BFC (2.7% vs. 3.6% for BFC and FSC, respectively; p=0.05). A second propensity-matched cohort study was published by Janson et al. in 2013, which used the same study population as Larsson et al., as described earlier. This study investigated the comparative risk of pneumonia and pneumonia-related mortality among a Swedish population with COPD who were treated with either BFC or FSC.(Janson et al. f3306) Following matching, 2,734 individuals were in each treatment arm. Each matched group was similar with respect to all measured baseline characteristics, including smoking status. This study found that the pneumonia rate (defined using hospital and primary care records) among patients treated with FSC was approximately 73% higher than that among patients treated with BFC (rate ratio 1.73, 95% CI 1.57 to 1.90). Similarly, they observed a 76% increased risk of pneumonia-related mortality among FSC users compared to BFC (HR 1.76, 95% CI 1.22 to 2.53).

Key Findings:
Two population-based, propensity-matched cohort studies in US and Swedish populations suggest that there may be a slightly increased risk of developing pneumonia and dying of pneumonia-related causes among individuals with COPD treated with FSC compared to those using BFC.

Adherence

Two studies investigated differential adherence to ICS+LABA combination therapies. In a Canadian matched cohort study by Blais et al. described previously,(Blais, Forget, and Ramachandran 1320-28) the authors examined a secondary outcome of treatment adherence in the year following treatment initiation, defined as the percentage of days with drug supply over the 1-year period. This study found no significant difference in adherence between new users of BFC (mean Medication Possession Ratio [MPR] 52.3%) and FSC (mean MPR 52.3% vs. 51.5%, respectively; adjusted mean difference -1.8, 95% CI -4.1 to 0.6). Similarly, Roberts et al. found comparable adherence patterns between BFC and FSC users over a 3 to 6 month follow-up period.(Roberts et al. 769-76) However, this study of COPD patients in the US (described earlier) found a slightly higher proportion of patients with an MPR over 76% among the FSC cohort compared to the BFC cohort (exact numbers not reported; $p<0.05$).

Key findings
Two cohort studies reported comparative adherence to ICS+LABA combination therapy as secondary analyses. In general, it appears that there are no major differences in adherence (as defined using medication possession ratios), although users of FSC may be slightly more likely to be highly adherent to therapy in the first 3-6 months compared to BFC users.

Fluticasone/salmeterol vs. Dual 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 the US, and investigated overall survival.(Mapel et al. 127-34)

Death

In 2007, Mapel et al. published a cohort study comparing survival among COPD patients in the US treated for at least 3 months with one of a variety of therapeutic options, including combined fluticasone/salmeterol inhalers, ICS+LABA dual therapy (use of both products separately, but simultaneously), ICS alone, LABA alone, and SABA alone (reference group).(Mapel et al. 127-34) The authors identified 866 FSC users and 525 ICS+LABA dual therapy users between September 2000 and August 2003. On average, patients treated with FSC were younger than other treatment groups (64.5 years vs. 67.6 years, FSC vs. ICS+LABA dual therapy), and had slightly less oral corticosteroid use in the baseline year (54.0% vs. 56.0%, FSC vs. ICS+LABA dual therapy). However, patients treated with ICS+LABA dual therapy had a higher number of inpatient COPD encounters (23.2% vs 16.1%, ICS+LABA dual therapy vs. FSC), suggesting that these patients may have more severe disease. Both FSC and ICS+LABA dual therapy groups were more likely to have a co-diagnosis of asthma (31.8% and 31.4%, respectively) compared to other exposure groups (range 17.9% to 22.9%; $p<0.001$). In a Cox proportional hazards model, each treatment group was compared to the referent group of SABA. Both

FSC (HR 0.61, 95% CI 0.45 to 0.83) and ICS+LABA dual therapy (HR 0.59, 95% CI 0.46 to 0.77) had a significant survival benefit compared to SABA, however no significant difference between treatment groups (e.g. FSC vs. ICS+LABA dual therapy) was found.

Key Findings

Evidence from one, small cohort study from the US suggests no differential survival among those treated with a combination ICS+LABA product (FSC) compared to those treated with ICS+LABA dual therapy.

Conclusions

Comparative observational studies of ICS+LABA combination products suggest that BFC and FSC are largely comparable products as it relates to COPD exacerbations and adherence to therapy. There is some evidence to suggest that BFC may be superior to FSC for some measures of COPD exacerbation, however many do not appropriately account for baseline differences in important confounders between groups which could influence these findings. Therefore, any differences in reported effectiveness should be interpreted with caution. Evidence from one large population-based studies suggests that there may be a significantly increased risk of pneumonia and related death among those treated with FSC compared to BFC, however another study investigating this question in a US setting found no difference in risk for most pneumonia-related outcomes investigated. Only one study compared an ICS+LABA combination product and dual therapy. This study suggested no survival difference between these groups.

Overall, the evidence in this area from observational studies is inconsistent and of varying quality. This body of research does not suggest any 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
Roberts et al.(Roberts et al. 769-76)	Propensity Matched Cohort Study	United States 3,385 BFC 3,385 FSC	BFC vs. FSC	COPD Exacerbations Pneumonia Adherence	• No significant differences in rates of all COPD exacerbation events or major COPD exacerbation events • The use of SABAs and ipratropium were significantly lower among BFC users compared to FSC users • No significant difference in rates of pneumonia-related hospitalizations or ED visits • Small, marginally significant lower rate of outpatient visits related to pneumonia among users of BFC • Comparable adherence over 3-6 month follow-up. • Slightly higher proportion of patients with an MPR over 76% among the FSC cohort compared to the BFC cohort	Large study Crude analyses only despite some differences at baseline. Industry-funded

Study Author	Study Design	Population	Comparison	Outcomes	Key Findings	Strengths/Limitations
Mapel et al.(Mapel et al. 60-68)	Propensity Matched Cohort Study	United States 3,852 BFC 3,852 FSC	BFC vs. FSC	Severe COPD Exacerbations	• No significant difference in rates of COPD-related hospitalizations or COPD-related ED visits between exposure groups over the 6 month follow-up	Large Study Key comparisons were pre-post analyses. Therefore, comparisons between drugs limited, and not well defined. Industry-funded
Larsson et al.(Larsson et al. 584-94)	Propensity Matched Cohort Study	Sweden 2,734 BFC 2,734 FSC	BFC vs. FSC	COPD Exacerbations	• Individuals treated with BFC had fewer COPD exacerbations per patient-year compared to those treated with FSC ($p<0.0001$) • Subgroup analysis among patients aged 60 years and older found consistent results	Long follow-up (3.5 years) Patients comparable at baseline after matching Industry-funded
Blais et al.(Blais, Forget, and Ramachandran 1320-28)	Matched Cohort Study	Canada 1,131 BFC 1,131 FSC	BFC vs. FSC	COPD Exacerbations Adherence	• No significant difference in primary outcome of any COPD exacerbation • Those initiating BFC were significantly less likely to have ED visits ($p<0.05$) or hospitalizations ($p<0.05$) for COPD. • No significant difference in adherence between new users of BFC and FSC.	Canadian Study Matching did not create comparable treatment groups; therefore findings may be biased due to unmeasured confounding Industry-funded

Study Author	Study Design	Population	Comparison	Outcomes	Key Findings	Strengths/Limitations
Janson et al.(Janson et al. f3306)	Propensity Matched Cohort Study	Sweden 2,734 BFC 2,734 FSC	BFC vs. FSC	Pneumonia Pneumonia-related mortality	• Pneumonia rate among patients treated with FSC was significantly higher than that among patients treated with BSC • Significantly increased risk of pneumonia-related mortality among FSC users compared to BFC.	Patients comparable at baseline after matching Industry-funded
Mapel et al.(Mapel et al. 127-34)	Retrospective Cohort Study	United States 866 FSC 525 ICS+LABA Dual Therapy 1,832 SABA	FSC vs. Dual Therapy (ICS+LABA) vs. SABA	Death	• Both FSC and ICS+LABA dual therapy had a significant survival benefit compared to SABA • No significant difference between treatment groups (e.g. FSC vs. ICS+LABA dual therapy) was found	Patients not matched; therefore findings may be influenced by unmeasured confounding Industry-funded

Appendix B: Medline Search Strategy

1. budesonide.mp. or exp Budesonide/ (3625)

2. formoterol.mp. (1413)

3. fluticasone.mp. (2907)

4. salmeterol.mp. (1975)

5. advair.mp. (39)

6. symbicort.mp. (133)

7. (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)

8. formoterol.mp. (1413)

9. mometasone.mp. (601)

10. zenhale.mp. (1)

11. (1 and 2) or 6 (547)

12. (3 and 4) or 5 (868)

13. (8 and 9) or 10 (26)

14. 11 and 12 (168)

15. 11 and 13 (1)

16. 12 and 13 (2)

17. 14 or 15 or 16 or 7 (179)

19. limit 17 to english language (165)

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: Definition of COPD Severity

COPD severity was assigned hierarchically as follows:

(1) Very severe – if individual meets criteria for very severe COPD
(2) Severe – if individual meets criteria for severe COPD and is not very severe
(3) Moderate – if individual is not very severe or severe

Very Severe COPD

Patients were classified as having very severe COPD if they met any of the following criteria:

- 1 or more hospitalizations in the previous 2 years with a most responsible diagnosis of a COPD-related respiratory disease; OR
- Use of oral corticosteroids for longer than 180 days in the previous 2 years; OR
- Lung reduction procedure in the previous 5 years; OR
- Currently on oxygen therapy

Severe COPD

Patients were classified as having severe COPD if they met any of the following criteria:

- 2 or more exacerbations in the previous 2 years; OR
- At least 1 unscheduled emergency department visit in the previous 2 years with a most responsible diagnosis of a COPD-related respiratory disease

Moderate COPD

Patients were classified as having severe COPD if they met the following criteria:

- 0-1 exacerbations in the previous 2 years

COPD Exacerbations

Exacerbations were defined as receipt of a prescription for an oral corticosteroid or respiratory antibiotic within 7 days of a physician visit for bronchitis, pneumonia, influenza, emphysema, asthma, or other chronic obstructive pulmonary disease.

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