ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

# Stakeholder Comments and Ontario Drug Policy Research Network (ODPRN) Response:

# ICS+LABA in Asthma

April 7th, 2014

30 Bond Street, Toronto ON, M5B 1W8 www.odprn.ca info@odprn.ca

## COMMENT

Please comment on how current clinical practice guidelines informed the pharmacoeconomic and reimbursement considerations of the ICS+LABA asthma class review.

***Response:*** *Current clinical practice guidelines were reviewed as part of the environmental scan and were considered in the reimbursement options. For example, all guidelines recommend the use of ICS+LABA, either as a combination inhaler or as two separate inhalers, for the management of patients with asthma, in particular those patients who are uncontrolled on inhaled steroid. A statement has been added to the report to state: "For patients 12 years of age and older who remain uncontrolled on low-dose ICS, the addition of a LABA is recommended, ideally in the form of a combination inhaler."*

## COMMENT

Please explain why the Draft Consolidated report of the ICS/LABA asthma class review includes comparisons between BFC and FSC when this comparison was not addressed appropriately in the systematic review, and is based solely on retrospective, observational & database studies (with all of their known limitations)?

***Response:*** *The consolidated report summarized the results of the Rapid Review team, as well as results from the Pharmacoepidemiology Team. The Pharmacoepidemiology Team conducted a review of the observational literature to evaluate 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. It is clearly stated in the consolidated report that the information on the comparisons between products is based on information from observational studies. As well a cautionary statement is included: Results of these studies should be interpreted with caution due to the possible impact of systematic differences in comparison groups leading to bias.*

## COMMENT

We respectfully request consideration be given to the addition of an appropriate disclaimer to the ICS+LABA asthma class review documents to reflect the limitations of the class review, and to ensure understanding that the views expressed therein do not necessarily represent the view of any national/provincial government, or manufacturer. Consideration should also be given to expand the disclaimer to include additional statements similar to those included in final CDEC recommendations issued by CADTH (e.g., "1. The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice. 2. CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document. 3. The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer."

***Response:*** *Thank you for your suggestion. We currently have a statement in our "Acknowledgement" section that states: "The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources and supporting organizations. No endorsement by SMH, ICES, CIHI, or the Ontario MOHLTC is intended or should be inferred." No further changes will be made.*

## COMMENT

Attempts to compare BFC single maintenance and reliever therapy (SMART) with fixed dose combination ICS/LABA products have been confounded by a lack of blinding and unspecified dose adjustment strategies. Additionally, most of the SMART trials included patients with uncontrolled disease at recruitment, which may confound true disease severity (Chapman, 2010).

***Response:*** *There is no reference to nor recommendation for SMART therapy in the consolidated report. No changes have been made to the report.*

## COMMENT

Based on the Canadian guidelines (Lougheed et al., 2010), in adults and children ≥ 12 years of age, the use of an ICS/LABA combination in a single inhaler is recommended if asthma is not adequately controlled with a low dose of ICS (250 µg or less of HFA beclomethasone equivalent). In support of this recommendation, it was noted that increasing the dose of the ICS in this patient population, often provides little added clinical benefit and increases the risk of potential adverse effects (Lougheed et al., 2010). The use of an ICS/LABA combination in a single inhaler is preferred over the use of separate inhalers because they preclude use of the LABA without an ICS, which can lead to increased risk of death and hospitalization (Ernst et al., 2006; Salpeter et al., 2006), are more convenient, and may enhance adherence (Lougheed et al., 2010). The 2010 AIM survey also indicated that patients are confused about the differences between controller and reliever medications and when to use each type of drug. The use of an ICS/LABA combination in a single inhaler simplifies the process for patients and ensures they receive the benefits of both medications

***Response:*** *It is beyond the scope of the consolidated report to provide detailed guidelines on the management of asthma. However, a statement has been added to the consolidated report regarding patients 12 years of age and older who remain uncontrolled on low-dose ICS (For patients 12 years of age and older who remain uncontrolled on low-dose ICS, the addition of a LABA is recommended, ideally in the form of a combination inhaler). Additionally, a statement has been added to the Environmental Scan report (under the guideline section) regarding the preference of combination inhalers vs. use of two single inhalers (A combination inhaler is preferred over the use of two single inhalers in order to prevent patient error, as LABAs should never be used alone (as monotherapy) for asthma).*

## COMMENT

A second overall concern about this study relates to transparency. Access to data used to make recommendations has been very limited. We have been told that this data will be available later, because researchers wish to publish their work under their own names. We find this totally unacceptable for public funds dedicated to the purpose of recommending reimbursement options for drugs that are important for our well-being and health.

***Response:*** *As outlined on our website, censored reports from each of the units will be made publically available subsequent to the completion of each drug class review. In order to maintain academic priority and to avoid jeopardizing potential publications of drug class review findings, each unit is provided with a 6 month period after the release of the censored reports to submit manuscripts for publication consideration. All uncensored reports will be publically released at the end of the 6 month period, if not submitted for publication. Note that the OPDP receives all*

*uncensored reports at the completion of the review.*

## COMMENT

A further general concern would be the pre-eminence of "control" over "severity" in this review. Current trends in asthma research are moving towards a more complex understanding of the importance of severity as well as control and this has been largely ignored.

***Response:*** *There were clinicians who were members of our Research Team who provided input on the outcomes that we included in our review. There has been some debate regarding asthma control or asthma severity in the classification of asthma (Humbert et al. Allergy 2007;62:95). It is acknowledged that asthma control is a more useful outcome for the management of patients than asthma severity. A change has been made to the Consolidated Report (first paragraph Challenges in Asthma Management) to read: The high cost of medications, fear of regular steroid use, lack of education about the purpose of maintenance medications, and poor perception of asthma control were all described by participants as barriers.*

## COMMENT

One glaring omission in this report regarding health equity is the prevalence of asthma among Ontario's First Nations population. Asthma rates are 40% higher among aboriginal Canadians. While the federal government retains responsibility for on-reserve First Nations, urban First Nations individuals face on-going health issues, including asthma for which Ontario remains responsible. Any change to asthma treatment that will lessen the availability of medication and the accessibility to pharmaceutical options will hit aboriginal Ontarians to a disproportionate degree.

***Response:*** *Thank you for your comments. A section has been added to the Health Equity Issues section in the consolidated report that outlines the prevalence of asthma in the Aboriginal community and the limitations of our data to identify issues in this population [The prevalence of asthma in Aboriginals is higher than in non-Native populations. According to the 2005 Community Health Survey, the prevalence rate of asthma among Aboriginals was higher than in the non-Aboriginal population (11.7% and 8.3%, respectively). A limitation of our pharmacoepidemiology research is that we were unable to stratify our data into Aboriginals and non-Aboriginals, and therefore are unable to determine the use of ICS+LABA products in this population].*

## COMMENT

According to the Ontario Lung Association's 2011 report "Your Lungs, Your Life", asthma costs the Ontario economy $1.6 billion in direct health care costs. We would like to respectfully point out that the cost estimates referenced in the "Consolidated Final Report" are grossly underestimated ($504-$648 million annually in Canada-it appears that these data were drawn from a 25-year-old study).

***Response****: Thank you for pointing this out. The sentence has been updated to include this information.*

## Qualitative Team:

### COMMENT

Will the manufacturers have an opportunity to comment on the Social Acceptability research?

***Response:*** *The results of the Social Acceptability research (Citizen's Panel) will be incorporated into the final reimbursement report. There is no opportunity for stakeholders to provide feedback on the Social Acceptability research.*

### COMMENT

Who is the Citizen's Panel comprised of and what is the process and goals of these meetings.

***Response:*** *The purpose of the Citizen's Panel is to capture the opinions and feedback of individuals from the general public. The ODPRN Citizen's Panel (CP) is comprised of members of the general public with approximately 1/3 of these members who are also a part of the Ministry of Health and Long Term Care's Citizen's Council (OCC). ODPRN CP members include retirees, students and working professionals, none of whom have any direct ties in the reviews. To gather viewpoints on the research and reimbursement options, we use a modified Delphi approach. Prior to the meeting, members are provided with a 4-5 page lay summary of the efficacy, safety, accessibility, and cost of the drug/drug class, and appendices containing detailed study findings. They are also provided with a survey and are asked rank the acceptability of each recommendation. During the meeting, the recommendations are further discussed in detail, questions are clarified, and the panel is then asked to re-rank the recommendation.*

### COMMENT

Can the ODPRN create 4-5 page lay summary of the each drug class review and make it publically available?

***Response:*** *The Knowledge Translation Team produces a one-page summary of the findings and recommendations for the lay public as well as another version for clinicians; these are posted at the time of the final report.*

### COMMENT

We believe the executive summary did not provide a fair-balanced summary of the content from the body of the report. The executive summary focused on cost-related insights and little attention was paid to adherence and access, for example, frequency of dosing; lack of understanding; ease of use; device consistency; patient support. In addition, the framework of the study and methodology imposed has substantial limitations that were discussed in the report body but not in the executive summary.

***Response:*** *We have revised the executive summary so that it is more representative of the key themes in the report. We have also added additional details about the limitations.*

### COMMENT

Page 7 includes a section title "Key Themes related to the Migraine Experience and the Treatment of Asthma with ICS/LABA"; we believe this is a typographical error.

***Response:*** *Thank you -this error has been corrected.*

## COMMENT

I found the results interesting, and was surprised by the small number of people interviewed. I had assumed there would have been more participants.

***Response:*** *Qualitative research studies tend to comprise smaller samples than quantitative studies. Currently, there are no guidelines that outline exactly how many participants are sufficient to ensure a robust qualitative analysis[1]. Generally, qualitative researchers make decisions about sampling based on factors such as:*

- *Feasibility – what is the time frame available for participant recruitment?*
- *Heterogeneity – how diverse is the group we are recruiting?*
- *Saturation of data – have we captured as many unique themes as possible about the phenomenon being studied?*

*As mentioned in the limitation section of our report, we reached saturation of themes about half-way through interviews. However, since we received many requests for participation in this work, we continued to interview and recruit a total of 17 patients and 7 physicians. It is important to highlight that most qualitative research studies do not operate on such short timelines –our team has made a significant accomplishment by recruiting 24 individuals in only 8 weeks. The National Centre for Research Methods in the United Kingdom has recommended that qualitative researchers who have 8-16 weeks for recruitment should aim for a sample of approximately 12[2]. An American study on qualitative methods also concluded that saturation of themes can occur after 12 interviews and as early as 6 interviews[1].*

## COMMENT

We are concerned with the lack of true and significant patient involvement in the study. Asthma is a complex condition and the patient journey is unique to every patient. Physician-reported patient experience is no substitute for direct patient engagement. The number of patients involved in such a study needs to be high given the different manifestations of the disease.

***Response:*** *We agree with your sentiment. Patient participants outnumbered physician participants in our study – they comprised approximately 71% of our total sample. As well, it should be noted that a patient representative was involved on the drug class review research team.*

- *Qualitative samples tend to be small, particularly for studies with short time frames. Qualitative research aims to achieve in-depth analysis with a small sample as opposed to other methods that gain breadth of experiences through bigger samples but don't allow researchers to probe root causes and underlying issues. We believe by talking one-on-one with patients, we have contributed more information about the patient experience and have involved them more highly in the study more than other methods allow. It should be noted that most drug class review frameworks do not include a qualitative research component with patients.*

## COMMENT

We have a concern about the singular use of exacerbations as an indicator of control without a full definition of what an exacerbation is, especially in the patient experience.

***Response:*** *In the sub-section "Patient perception of disease" we have explained that patients and clinicians may have various interpretations of the concept of control. We have also referred to different indicators that may be considered in the discussion of control such as frequency of rescue inhaler use, night time awakenings and significant lifestyle modifications. It is important to note that qualitative results are representative of what the interviewees believe or perceive to be important; therefore, reported indicators of control were not defined by us, but by what the interviewees reported and defined themselves as indicators of control.*

## COMMENT

We would be interested to see more regarding the qualitative analyses of patient interviews and the nature of their "specific experiences and perceptions relevant to funding policies." Patients are rarely experts on funding policies. We would specifically like to know how the challenges in asthma management were assessed from the patients' perspective, especially since it is acknowledged that they were primarily discussed with clinicians. While the cost of medications, fear of steroids, misunderstandings about maintenance medications and poor perception of asthma severity are all problems we have identified, we place their roots more in a failure of physicians to communicate than patients to understand (and hence are involved in research of motivational interviewing to improve patient communications). It is not our general experience that patients rely on reliever medications primarily because of the cost of controllers. Rather, it is more often the failure of patients to recognise the importance of controlling their chronic episodic illness.

***Response:*** *We understand that most patients may not be experts in funding policies; as such we do not ask them directly about funding policies but consider the policy-relevance of our findings during analysis and interpretation of the data. As we mentioned in the limitations section of this report, most of the physicians we interviewed were either advocates for asthma patients or had a special interest in asthma. They were largely in favor of asthma patients – especially patients who not have coverage for medications. The vast majority of our asthma patient participants did not have financial barriers to accessing medication. However, since the focus of this study is on financial access through the public payer system, we felt that it was important to highlight the findings related to those who do not have drug coverage, as affordability can impact which drugs are prescribed and ultimately used. From a health equity perspective we cannot discount experiences that patients may have had related to cost of drugs. We did ask patients to discuss asthma management from their perspective and we have interspersed these findings throughout this section. We have also highlighted the need for improved physician communication under the sub-section "patient perception of disease"—by pointing out that if physicians do not ask patients the right questions they will not be able to determine the patient's true disease state. Overall, we do not believe that we have left out any pertinent information. It is important to keep in mind that qualitative data is not representative of the general population of individuals from which our study sample was drawn. This is why you may find that some of the findings may be different from your general experience. As well, this qualitative study is just one piece of this drug class review and its findings need to be interpreted in the context of the larger review.*

References:

1. Guest, Greg, Bunce, Arwen, and Johnson, Laura. How many interviews are enough? *An experiment with data saturation and variability*. Field Methods, Vol. 18, No. 1, (2006) 59–82
2. Baker, Sarah Elsie and Edwards, Rosalind (2012) *How many qualitative interviews is enough.*

# Pharmacoepidemiology Report

## COMMENT

We believe the report includes inappropriate conclusions based on the data and a potential misrepresentation of asthma claims data and the GINA guidelines. On page 3, the authors stated "*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 (20-30% and 20-30% respectively).*" Since the numerical estimate was the same for each therapy, it is not clear how the conclusion of differential time on therapy was reached. Additionally, given the seasonal impact on some individuals with asthma, it may not be reasonable to assume that all ICS/LABA users would be on therapy one year after initiating therapy.

***Response:*** *Thank you for your comment. As to not preclude future publishing of the analyses we had to censor the results of this analysis. The proportion was lower for Advair users and but to offer further insight we will make the change in our report to offer more information for these results. The statement will now read: "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 (20-25% and 25-30% respectively)" . Further changes will be made on p3, p.30 and p.32.*

- *Regarding the seasonal impact comment, we have defined continuous use by looking 180 days for the next prescription, which is a less restrictive approach to define continuous use. We will add your comment into our summary to give awareness to the seasonal impact which may affect persistence on therapy. Thank you.*
- *Addition and revisions on page: p 3, 30, 32, 34*

## COMMENT

Because trends in provincially funded ICS-LABA combination products were conducted using ODB claims data, it is difficult to identify users who are truly asthmatic rather than those with COPD who may be accessing these drugs via the existing LU 330 code for asthma, which is acknowledged by ODPRN in the ICS/LABA COPD Class Review and the Draft Reimbursement Options document. It is not clear if a strategy was employed to identify claims associated with a diagnosis of asthma. If not, it is likely that the data represents use and claims for patients with both asthma and COPD.

***Response:*** *Thank you for your comment. Provincial comparisons were made among all users, since we do not have Asthma or COPD diagnosis information for the provinces other than Ontario.*

- *In the Ontario specific analyses, we have identified when we have presented data among asthma patients. The ODB data was linked to the ICES asthma*

*cohort (Ontario Asthma Database) to gather diagnosis information. Please see the data sources section of the report (p8) which outlines how the asthma cohort was created. ("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 AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying patients with physician-diagnosed asthma in health administrative databases. Can Respir J 2009;16(6):183-188.))*

- *With administrative databases there is always the potential for misclassification which has been outlined in the limitation section (p33).*

## COMMENT

We disagree with the statement on page 36 which concludes that "*Significant difference between treatment groups, favouring BFC, were found among the two studies conducted outside of the UK.*" As noted by ODPRN, in one of these studies this result was not statistically significant after adjusting for confounders. Consequently, it is inappropriate to make the statement above. In fact, based on the large population based cohort studies reviewed, 3 of 4 studies indicated that no significant differences existed in the rates of exacerbations, based on hospitalizations, between BFC and FSC users. This should also be corrected in the corresponding section of the consolidated report.

***Response:*** *Thank you for your comment. As both studies by Blais et al. and Aballea et al. cite differences between products in their conclusions, we felt it was important to review what findings are cited in the literature. It is also important to appraise the evidence. We are concerned with the inconsistency in results found in the literature. We agree that differences between study arms may have led to the cited differenced in these studies. We have added a statement that reads "Results of these studies should be interpreted with caution due to the possible impact of systematic differences in comparison groups leading to bias."*

- *Addition and revisions on page: p 36*

## COMMENT

At times this report refers to the prescribed treatment step, which was derived from the GINA Strategy for asthma management and prevention. What was the rationale for referring exclusively to GINA rather than also commenting on the Canadian Thoracic Society Asthma Treatment Guidelines? Appendix D appears to suggest that the GINA guidelines Step 3 treatment preference is for an increased dose of ICS monotherapy, however the GINA statement reads "*For patients with persistent symptoms and/or exacerbations despite low dose ICS, consider step up but first check for common problems such as inhaler technique, adherence, persistent allergen exposure and comorbidities. For adults and adolescents, the preferred step-up treatment is combination ICS/long-acting beta2-agonist (LABA).*" (GINA 2014).

***Response:*** *Thank you for your questions and comments. We used the GINA guideline based on clinical recommendations and input. We asked stakeholders for input on this piece extensively during the drug class review as this is a novel piece. We received no input from stakeholders and decided to define this using the GINA guidelines. This is a novel and crude measure of treatment step and it has limitations which are noted in the limitation section of the report (p.33). Although the preferred step-up treatment is combination therapy, the guidelines still include ICS dosing in the treatment steps. Thus, we have incorporated this into our analysis. We have made no suggestions on the GINA preference step; however we will add a footnote to the appendix to avoid any confusion. Thank you.*

- *Addition and revisions on page: p 46*

## COMMENT

Depending on how accurately COPD patients are identified, the spending on ICS+LABA FDC for asthma may be overestimated. As noted in the ODPRN class review on the use of ICS/LABA combinations for COPD: "Ontario physicians use the asthma code to prescribe ICS/LABA combinations to their COPD patients". Hence, the model should ensure that COPD-related expenditures are removed for each product. This requires patient-level data analysis using past/current COPD-specific medication as a proxy for disease. Moreover, given that some products may be preferred by physician for the treatment of COPD versus others in asthma, this analysis should be done at the product level. Not enough detail is provided in the draft report to appreciate if this was done.

***Response:*** *Thank you for your comment. Please see the data sources section of the report (p.8) which outlines how we defined the asthma cohort (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 AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying patients with physician-diagnosed asthma in health administrative databases. Can Respir J 2009;16(6):183-188.)*
- *This cohort was used to present costs among asthma patients in 2012 (Exhibit 11).*
- *With administrative databases there is always the potential for misclassification which has been outlined in the limitation section (p33).*

## COMMENT

How can you ensure that patients are defined appropriately by disease type (asthma vs. COPD)? There is concern that perhaps the data from COPD patients may contaminate the data for asthma patients. We find it interesting that over half of the combination therapies in Ontario are paid for through the OPDP, which leads us to believe this is largely COPD data. Our patient surveys have consistently indicated that approximately 75% of asthma patients have private

drug plan coverage, approximately 15% have public coverage and about 10% have no coverage.

***Response:*** *Thank you for your comments. This data was collected from IMS and presented for all users, regardless of diagnosis, since IMS does not have information on user diagnoses. This is the best available data we had access to for this study.*

a. *Please see the data sources section for more information (p.7) "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."*

## COMMENT

We are interested in the increase of ICS+LABA usage between 2000 and 2012. We also know that in this same period hospital treatment and admissions have gone down. This potential co-relation has not been brought into this study.

***Response:*** *Thank you for your comment. This was not in the scope of the question we were asking, however may be further explored in the future.*

## COMMENT

While we do not question the adherence to combination therapy after one year, we are interested to know how this data was obtained and if it is new data or data that has been acquired from another study. The issue of adherence is far more complex than one device or agent over another in a chronic, episodic and often seasonal disease such as asthma.

***Response:*** *Thank you for your question. In the methods section we have outlined our approach to defining adherence (p10) "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."*

- *This is based on new data that we analyzed for this specific drug class review.*

## Systematic Review Team

### COMMENT

How are exacerbations defined?

***Response:*** *Severe Exacerbation was defined as: worsening of asthma symptoms that may require hospitalization, emergency department visits, or treatment with oral steroids and/or antibiotics.*

*Moderate Exacerbation was defined as: worsening of asthma symptoms that may require use of rescue medication, or unscheduled visits.*

### COMMENT

Although the ODPRN has acknowledged that they could not perform adjustments for potential confounders and effect modifiers such as duration of treatment, definition of outcomes, history of previous exacerbations, and disease severity due to limited timelines, we believe that these adjustments are a key component of rigorous and robust scientific methods and could improve the interpretation of results and the subsequent conclusions. In the absence of adjustment for these variables, more information about the distribution of potential effect modifiers across the different treatment comparisons in the network would have been useful, along with the $I^2$ values for the test of heterogeneity.

***Response:*** *This is a rapid review and due to the time limitations, we were unable to conduct any sub-group analyses. We did conduct formal tests for heterogeneity using the node-splitting method and did not identify any significant heterogeneity in our analyses. This method does not give an $I^2$ value; $I^2$ values are derived from traditional pairwise analysis and NMAs do not assess heterogeneity in the manner.*

### COMMENT

Few trials were designed and powered to assess exacerbations and we believe it would have been informative to conduct a subgroup analysis of those studies which were appropriately powered for exacerbations.

***Response:*** *Unfortunately due to the limited timeline associated with conducting a rapid review we were not able to conduct subgroup analysis for this review.*

### COMMENT

NNT/NNH should be considered as an ancillary measure and should be presented in the context of the actual proportions, relative benefit and a measure of variability. Although ODPRN has previously acknowledged that NNT/NNH measures are only used to help put the results into context, NNT/NNH data continues to be presented in isolation. To fulfill the goal of providing balanced, evidence-based data for policy decision makers, we believe that NNT/NNH data should not be presented in isolation.

***Response:*** *In order to put our results into context, we calculated the number needed to treat (NNT) or number needed to harm (NNH). Note that the OPDP receives the full uncensored*

*reports upon completion of the reviews.*

### COMMENT

We note Breo Ellipta is included in the list of medications included in the rapid review. *Breo Ellipta* is not indicated for the treatment of asthma, therefore, we respectfully request any data associated with *Breo Ellipta* be excluded from the report.

***Response:*** *We have noted in the consolidated report that Breo Ellipta is only indicated for COPD. However, we realize that some prescribers may use Breo Ellipta in the management of patients with asthma. As well, there are published studies using Breo Ellipta for asthma. Similarly, Zenhale, which is not indicated for the management of patients with COPD, was also included in our review of ICS+LABA for COPD.*

### COMMENT

A note should be made about the use of the term "chronic asthma" in this section. Asthma is defined as a chronic illness so we are not sure what is meant by differentiating chronic asthma from some other form. Perhaps what is meant is the experience of persistent symptoms, or therapy-resistant asthma or what has variably been termed as chronic severe asthma, steroid-dependent asthma, difficult-to-control asthma, and refractory asthma.

***Response:*** *We focused inclusion of trials of patients with chronic asthma (as defined by the study investigators) who experienced persistent symptoms.*

## Environmental Scan

### COMMENT

We note “fluticasone” is used to represent the ICS contained in both Advair and *Breo Ellipta* in several instances. It is important to note the ICS contained in *Advair* is “fluticasone propionate” (FP) and the ICS contained in *Breo Ellipta* is “fluticasone furoate” (FF). Since FP and FF are structurally distinct drug substances with different clinical profiles, reference to “fluticasone” should be corrected throughout the class review documents so that reference is made specifically to either FP or FF, as appropriate.

***Response:*** *This has been corrected throughout the Environmental Scan report as well as the Consolidated Report.*

### COMMENT

In the event this document is consulted in future and the drug programs no longer reflects current status, the information included in this section of the report should indicate the status of programs “as of” a particular date.

***Response:*** *A note has been added to the table (in both the Environmental Scan and the Consolidated Report) to reflect when the table was compiled.*

### COMMENT

The section on DPIs should be revised to accurately represent the DISKUS inhaler; and the inclusion of COPD information in this section is not clear.

***Response:*** *The section has been revised to include Advair Diskus inhaler. As well, information exclusive to COPD has been deleted from this section.*

## COMMENT

The discussion of DPIs on page 30 erroneously states DPIs must be "*loaded before each inhalation, and this may require opening blister packs that contain the medication capsules*". This is not true of all DPIs, such as the *DISKUS*, which requires no pre-loading by the patient.

***Response:*** *This statement has been corrected to: Single-use DPIs (e.g., Spiriva HandiHaler) must be loaded before each inhalation, and this may require opening blister packs that contain the medication capsules; no ICS+LABA approved for management of asthma in Canada is available as a single-use DPI . Advair Diskus and Symbicort Turbuhaler are multi-dose DPIs and contain more than one dose of the drug. Regardless of whether the device is single- or multi-dose DPI, there is a potential to use the DPI device incorrectly, including failure to exhale before actuation and failure to hold the breath after inhaling.*

## COMMENT

Several references are made to COPD in this section. COPD patients have different inspiratory flow rate capabilities and other demographic characteristics that may not be transferable to asthma, which is the subject of this class review. Therefore, it is not clear why this COPD information has been included.

***Response:*** *Thank you for your comment. Information exclusive to COPD has been deleted from this section.*

## COMMENT

We disagree with the suggestion that *"single-therapy inhaler with budesonide-formoterol in patients with moderate or severe asthma may result in a reduction in the rate of exacerbations".*

***Response:*** *Systematic review and meta-analysis, including two Cochrane reviews, have shown that single-therapy inhaler with budesonide-formoterol may result in reduction in the rate of exacerbations, compared to current best practice and combination inhalers (steroid+LABA plus SABA).*

## COMMENT

SMART therapy is not a therapeutic alternative to other ICS/LABA combination but a different schedule of administration of BFC. According to both Canadian and International asthma guidelines, SMART therapy is an option (not a preferred recommendation) versus the use of SABA as a rescue medication. If it is used, it is in exacerbation prone adults with moderate/severe asthma and poor control while on regular dosing of ICS/LABA combination as a controller (Lougheed 2012, GINA 2014). Numerous comparative studies of the SMART approach with the ICS/LABA maintenance therapy and ICS monotherapy exist. Almost all of these studies were designed to show the difference in favour of SMART. Patients recruited into SMART trials often had asthma that was uncontrolled or undertreated on ICS at baseline. The results of these studies have to be interpreted with caution. It is not an appropriate clinical approach to leave patients in one arm undertreated if they are not controlled. The appropriate clinical management is to increase therapy in uncontrolled patients as was done in the GOAL

study (Bateman 2004). Currently there is insufficient evidence that the symptom driven SMART approach is superior in the management of asthma compared to the conventional physician prescribed and adjusted maintenance therapy with a fixed combination of ICS/LABA. The study by Papi and colleagues was the first to investigate this and found that as-needed budesonide and formoterol (SMART) was less effective than guideline-recommended maintenance treatment with respect to the primary outcome of time to first treatment failure measured at 1 year; a composite event measure based on health care use, additional steroid or high rescue medication use, nocturnal awakenings, or withdrawal from the study by the doctor or because of patient dissatisfaction (Papi 2014). Recent evidence from UK pharmacy databases indicate that approximately half (53%) of patients given a SMART prescription were still prescribed a short-acting reliever versus 82% of patients without a SMART prescription (DiSantestefano et al, 2014). In another six-month study, 43.6% of patients with "and when required dosing" (61 of 140 patients) received a SABA (Boyter 2011). In his critique of SMART data, Chapman concludes that guideline defined asthma control seems to only be achieved in a minority of patients (17.1%), using the SMART approach, in contrast to the reported reductions in severe exacerbations (Chapman 2010). Many questions still remain unanswered regarding the SMART approach including long-term outcomes, and whether any benefit is seen in partially controlled or controlled patients who use their as-needed inhalers less frequently than the participants at baseline in the SMART studies.

***Response:*** *It is acknowledged that the guidelines recommend SMART therapy as an option for specific patient populations (i.e., those prone to exacerbations and who have uncontrolled asthma). A sentence has been added to the introductory paragraph: The Canadian guidelines and GINA 2014 guidelines include the use of a single inhaler of BFC as a reliever and a controller as an option for select patient groups.*

- *The study by Papi and colleagues compared regular versus as-needed BFC for patients with moderate asthma. Note that for the randomized part of the study, patients assigned to the as-needed BFC did not receive regular maintenance therapy with BFC; therefore, this study did not compare "SMART" therapy with regular maintenance BFC.*

## COMMENT

Despite the fact that Canadian guidelines (Lougheed et al., 2010) recommend in adults and children ≥ 12 years of age, the use of an ICS/LABA combination in a single inhaler if asthma is not adequately controlled with a low dose of ICS (250g or less of HFA beclomethasone equivalent), several surveys have indicated that asthma is sub-optimally controlled in Canada. Exacerbations were also a major issue then and were the main reason for patients to be classified as uncontrolled, with 81% of patients with uncontrolled disease reporting an exacerbation versus 16% with controlled disease (P<0.01). Exacerbations were the major driver of costs associated with asthma.

***Response:*** *A statement has been added to the background section, last paragraph: In a survey conducted in Canada, asthma control and management remained suboptimal with approximately 50% of patients with uncontrolled asthma. (McIvor et al. Can Fam Phys 2007;53:672-7)*

## COMMENT

This is a helpful summary of Ontario, Canadian and International guidelines and practice of treatment for asthma. In general, it is supportive of our position that ICS+LABA combination therapy is an important component in the toolbox of any clinician treating someone with asthma and should be available, accessible and reimbursable under public drug plans.

***Response:*** *Thank you for your comment.*

# Pharmacoeconomics Report

## COMMENT

We believe the *de novo* economic evaluation has not incorporated all of the benefits and risks of ICS/LABA combination therapy and high dose ICS, and there are several clinical concerns that the "*...optimal strategy considered was introducing LABA to patients when they were uncontrolled with high doses of ICS.*" The model only captures treatment effect for rate of exacerbation. This may bias the result in favour of the ICS mono therapies. The benefits of ICS/LABA compared to a higher dose ICS exceed reducing exacerbations.

***Response:*** *It is unclear what is meant in this comment as "clinical concerns". It would be useful if it could be clarified what extra benefits that should be incorporated within the model. It should be noted that incorporation of more than one outcome within an economic evaluation can frequently lead to double counting of benefits from therapy thus biasing results in favour of therapies. We adopted the most frequently used primary outcome measure from clinical trials (exacerbations) as the outcome measure of choice for our evaluation which is consistent with most previous studies.*

## COMMENT

Uncontrolled asthma is responsible for the majority of the asthma-related cost (Bateman 2006, Sadatsafavi 2010). Asthma control has been shown to be achieved more rapidly and at a lower ICS dose with combination therapy (Bateman 2004). It is important to account for this comparative benefit of ICS/LABA therapy in the model to fully characterize the economic impact of asthma control and the additional therapeutic values provided by combination products. It was noted in a recent Cochrane Review (Ducharme et al. 2010) and the CTS 2012 asthma guidelines that ICS/LABA therapy led to a reduction in exacerbation, improvement in lung function (eg., Morning and evening PEF) and symptoms, reduced use of rescue beta$_2$ agonists, decreased time to achieve well-controlled asthma and fewer withdrawals due to poor asthma control compared to treatment with a higher dose ICS (Lougheed 2012).

***Response:*** *Some of the comments made by the reviewer are not consistent with findings from the ODPRN systematic review. As above, incorporating more than one outcome within an economic evaluation can frequently lead to double counting of benefits from therapy thus biasing results in favour of therapies. The lack of consistency in definition and measurement of "asthma control" in clinical trials makes modeling of this outcome within a class review fraught with difficulties.*

## COMMENT

In the base case of the *de novo* model, the disutility of ICS was assumed to be 0%, which resulted in an estimated $322,684 per QALY if LABA is introduced to those uncontrolled on medium dose ICS versus those uncontrolled on high dose ICS. Exploratory analysis including an increasing disutility of ICS resulted in an ICUR of $6,373 per QALY. The significant variability in results observed in this exploratory analysis warrants further work to address the disutility of high dose ICS in the de novo model. Additionally, caution should be taken in the interpretation of the results given the lack of certainty and robustness in the model results.

***Response:*** *We agree that caution should be taken in interpreting the results but emphasize this is due to the weak evidence base with respect to certain parameters. We are not aware of any published literature that shows there is a disutility associated with higher doses of ICS and if this were the case it should manifest in terms of the clinical condition of patients. We are not able within the confines of the class review to conduct primary research. Without such direct evidence of the effect of ICS dosage on utility we feel that the analysis we conducted with respect to this should be considered exploratory.*

## COMMENT

The probability of stepping down in therapy was assumed constant for all treatment options in this de novo model. This may not be a good representation of real treatment and may bias results. ICS/LABA therapy has been found to be superior to ICS mono therapy for symptom improvement and time to achieve good asthma control (Bateman 2004). Given that step-down occurs when asthma control is achieved for a period of time, the probability of stepping down would be higher and the time from initiation of therapy to stepping down would be lower for patients on ICS/LABA therapy. The differentiation in this variable should also increase the overall QALY in the strategies which introduce ICS/LABA therapy earlier since patients spend more time in a controlled state while the overall drug and healthcare costs are reduced.

***Response:*** *We have added a sensitivity analysis to assess whether increasing the probability of step-down would impact the base results. Assuming a doubling of the probability of stepdown with combination therapy compared to ICS does lead to changes in ICERs but not sufficient to reverse the conclusions of our analysis. For ICS+LABA to be cost effective if introduced after failure of medium dose ICS, the probability of stepdown with combination therapy would have to be 19 times higher than for ICS. The results of this sensitivity analysis have been added to our report.*

## COMMENT

The model does not capture adherence rates for different therapies or explore this variable through sensitivity analysis. In other chronic conditions, adherence to treatment has been recognized as an important factor affecting real-life effectiveness of asthma treatment (Marceau 2006, Horne 2006, Cerveri 1999, Delea 2008). Increasing adherence to treatment has been identified as an essential component of asthma patient management, leading to improved patient outcomes and reducing health care utilization. Adherence information from the pharmacoepidemiology analysis should be incorporated into the model to provide a robust economic evaluation.

***Response:*** *Good quality information is difficult to obtain and we recognize that randomized controlled clinical trial information may not be the best source for such information thus there is limited evidence to support any differences in withdrawal. Adherence data are available from the pharmacoepidemiology report for dual and combination therapy but not for ICS therapy.*

## COMMENT

The model has not incorporated any adverse events related to the various treatment options. In conjunction with the lack inclusion of disutility related to high dose ICS; this may contribute to uncertainties in the model. The long-term use of high-dose ICS therapy has potential to cause systemic side effects- impaired growth in children, decreased bone mineral density, skin

thinning and bruising, cataracts, osteoporosis, and fractures. Additionally, hypothalamic-pituitary-adrenal-axis suppression is correlated with the occurrence of systemic side effect of high dose ICS (Dahl 2006, Rossi 2007). These findings suggest that there is a disutility associated with high dose ICS and caution should be considered.

***Response:*** *There is a lack of data for modelling the impact of high-dose ICS in terms of disutility. This is evident by the lack of inclusion of such data in previous economic evaluations. We did include a sensitivity analysis which highlights how the results may change through the incorporation of such a disutility.*

## COMMENT

In the Systematic Review report, the outcome of exacerbation was not specified to whether it is GP, ER, or hospitalization. Given the three HCRU have different costs in the model, it is unclear how the cost is applied when a patient exacerbates.

***Response:*** *Data on the assumed distribution of exacerbations by type and their associated costs and disutilities is provided in Table 5 of the report.*

## COMMENT

Although a cost of dispensing a treatment was included in the model, it was unclear in the report on how often the dispensing fee is applied (ie., every quarter or monthly).

***Response****: Thanks for pointing this out. Costing was based on markup and dispensing fee being added on each individual puffer. This has been clarified in the report.*

## COMMENT

The ICERs reported seem high. It is hard to appreciate the conclusions of the pharmacoeconomic analysis with the very high level information provided. More details on the methodology would allow for a proper appraisal.

***Response:*** *The report details the structure of the model, the transition probabilities, costs and utilities. Without clarification from the stakeholder it is unclear where further details to allow clarity are required. We feel that the details provided would be sufficient for someone to replicate our analysis.*

## COMMENT

Many physicians may introduce a LABA separately earlier in the course of treatment which may diminish the potential estimated savings and in fact increase costs to the system. Furthermore, patients would need to manage 2 agents (reliever & controller) which may lead to suboptimal use of agents and asthma control.

***Response:*** *We agree. The potential cost savings will be offset by many different changes in physician practice such as use of separate inhalers. We did explore the use of higher dose combination products in our analysis and qualified our findings to suggest that little cost savings may be realized.*

## COMMENT

The use of an ICS/LABA combination in a single inhaler is preferred over the use of separate inhalers because they preclude use of the LABA without an ICS, which can lead to increased risk

of death and hospitalization (Ernst et al., 2006; Salpeter et al., 2006), are more convenient, and may enhance adherence (Lougheed et al., 2010).

***Response:*** *We do agree that the use of separate inhalers would likely lead to cost increases rather than savings. It was not the intention of our budget impact analysis to explore the clinical consequences of the use of LABA as a monotherapy, as it is unclear the likelihood that such practice would occur.*

## COMMENT

If low and medium dose ICS+LABA combinations would not be funded, many physicians may continue using both separate agents upfront which may diminish the potential savings and in fact increase costs. As well, some patients would need to manage 2 agents (reliever & controller), which may lead to suboptimal use of agents and asthma control. In patients not adequately controlled, ICS/LABA combination in a single inhaler is preferred over the use of LABA & ICS taken separately.

***Response:*** *As above, we agree. The potential cost savings will be offset by many different changes in physician practice such as use of separate inhalers. We did explore the use of higher dose combination products in our analysis and qualified our findings to suggest that little cost savings may be realized.*

## COMMENT

What is more troublesome is that the savings that are forecast even at the best case scenario may be completely offset and even more so by increased primary, specialist, emergency room and hospital admissions costs due to increased levels of asthma symptoms.

***Response:*** *The budget impact analysis, as is typical of such analyses, focuses solely on the costs to the public drug programs. However, the de novo economic evaluation detailed in Appendix B does address this issue and illustrates that such costs are not sufficient to offset the higher costs of combination products.*

References


1. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline- defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Am J Respir Crit Care Med. 2004;170(8):836–844.
2. Bateman ED. The economic burden of uncontrolled asthma across Europe and the Asia-Pacific region: can we afford to not control asthma? Eur Repir Rev 2006; 15(98):1-3
3. Boyter AC, Ford NH, Zlotos L. Audit of budesonide/formoterol prescribing for asthma in community pharmacy in the U.K. Respir Med. 2011;105:864–8
4. Cerveri I, Locatelli F, Zoia MC, et al. International variations in asthma treatment compliance: the results of the European Community Respiratory Health Survey (ECRHS). Eur Respir J 1999;14:288-94.
5. Chapman KR, Barnes NC, Greening AP, et al Single maintenance and reliever therapy (SMART) of asthma: critical appraisal. Thorax 2010;65:747–52.
6. Dahl R. Systemic side effects of inhaled corticosteroids in patients with asthma. Respiratory Medicine 2006 Aug; 100(8):1307-17.
7. Delea TE, Stanford RH, Hagiwara M, Stempel DA. Association between adherence with fixed dose combination fluticasone propionate/salmeterol on asthma outcomes and costs*. Curr Med Res Opin 2008;24:3435-42.
8. DiSantostefano etal. Profiling of single maintenance and reliever therapy (SMART) dosing instructions of budesonide/formoterol (BFC) in clinical practice. Poster publication
9. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled steroidsversus higher dose inhaled steroids in adults and children with persistent asthma.Cochrane Database of Systematic Reviews 2010, Issue4. Art. No.: CD005533. DOI: 10.1002/14651858.CD005533.pub2.
10. GINA 2014 Global Initiative for Asthma. Global strategy for asthma management and prevention. www.ginasthma.org . 2014. Ref Type: Online Source
11. Horne R. Compliance, adherence, and concordance: implications for asthma treatment. Chest 2006;130:65S-72S.
12. Lougheed M, Lemiere C, Ducharme F, et al. Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults. Can Respir J 2012; 19:127-164
13. Marceau C, Lemiere C, Berbiche D, et al. Persistence, adherence, and effectiveness of combination therapy among adult patients with asthma. J Allergy Clin Immunol 2006;118:574-81.
14. National Heart Lung and Blood Institute. The National Asthma Education and Prevention Program (NAEPP) Guidelines for the Diagnosis and Management of Asthma. 2007; http://www.nhlbi.nih.gov/guidelines/asthma/index.htm.
15. Papi A, Marku B, Scichilone N, et al for the AIFASMA Study Group. Regular versus as-needed budesonide and formoterol combination treatment for moderate asthma: a non-inferiority, randomised, double-blind clinical trial. Lancet Respir Med 2014; published online Dec 4. http://dx.doi.org/10.1016/S2213-2600(14)70266-8.
16. Rossi GA, Cerasoli F, Cazzola M. Safety of inhaled corticosteroids: Room for improvement. Pulmonary Pharmacology & Therapeutics 2007; 20:23-35.
17. Sadatsafavi M, Lynd L, Marra C, Carleton B. Direct health care costs associated with asthma in British Columbia. Can Resp J 2010; 17:74-80