ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

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

Reimbursement Options Report

April 7th, 2014

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COMMENT We agree with ODPRN statement (page 14, Exhibit 3) that due to the limited evidence available for the current review of the LAMA+LABA class, no recommendation for listing of LAMA+LABA combination products for OPDP will be made. Given the conclusion above, both the clinical and the economic assessment of the LAMA+LABA class should be removed from the final ODPRN final reports. In particular, we reiterate that the correct dosing for the LAMA+LABA class should be considered in the BIA base case scenario and not added as a scenario in the sensitivity analysis. Therefore all the BIA conclusions for the LAMA+LABA should be corrected accordingly.

Response: *Final LAMA for COPD reports, which includes LAMA+LABA for COPD, were posted on the ODPRN website in mid-January. Comments from stakeholders were taken into consideration for the final reports. Since these reports presented the results of the studies that were conducted by the research teams, no further changes will be made to the reports. Note that reimbursement options are not included in the final LAMA for COPD reports, but will be posted upon completion of this current review.*

- *The reimbursement criteria for LAMA+LABA class in Appendix E has been removed from the final report. As well, factors to consider for reimbursement, Exhibit 3, and assessment of reimbursement options for LAMA+LABA products have been removed from the final report.*

COMMENT Despite the conclusion that no recommendation for listing of LAMA+LABA combination products for OPDP will be made, the draft Reimbursement Options Report is proposing reimbursement criteria for the LAMA+LABA class in Appendix E (page 22). In addition, the proposed criteria is not aligned with the economic assessment as the BIA has assumed a general benefit criteria for the class (Pages 2,13,109, and 133 of the draft LAMA-PE report). Therefore there was no evidence in the draft reports that lead to the limited use criteria for LAMA+LABA proposed in Appendix E.

Response: *The reimbursement criteria for LAMA+LABA products in Appendix E has been removed from the final report. As well, factors to consider for reimbursement, Exhibit 3, and assessment of reimbursement options for LAMA+LABA products have been removed from the final report.*

COMMENT We disagree with the proposed reimbursement option C for the LAMA class: General Benefit (preferential listing) (p.5 and p.14) due to the following: "Efficacy: When LAMA products were compared to each other, no statistically significant differences were observed." (page 13) "Aclinidium was cost-effective compared to glycopyrronium and tiotropium, although there is uncertainty over this finding" (page 14).

Response: *Due to the uncertainty over the findings in the cost-effectiveness analysis for aclidinium compared to glycopyrronium and tiotropium, option C (general benefit with preferential listing) has been removed from the final report.*

COMMENT Describe how the limitations of the class reviews will be disclosed throughout the relevant sections of the Reimbursement Options document.

Response: *Limitations will not be disclosed explicitly in the Reimbursement Options document. However, links are provided in the document to the original reports, which describe the limitations for each of the reports.*

COMMENT In Appendix 1, Option D, the budget impact column includes the following text: COPD: ↓2.7% ($3.7 million)** †† . Please clarify what the †† footnote refers to, as this symbol does not appear below the table.

Response: *This was an oversight on our part. This will be removed in the final report.*

COMMENT Was any consideration given to the funding of spacers? While there are many studies about inhaler technique being key to the efficacy of inhaled medications, no attention has been given to the use of spacing devices for improved efficacy and whether or not they should be part of the ODPB.

Response: *The objective of the ODPRN review is to provide recommendations for the OPDP. It should be noted that the OPDP does not fund any devices, including spacers. The drug class review undertaken by the ODPRN did not include a review of the evidence for spacers. Therefore, no recommendation can be made for spacers. However, a comment will be added to the final report recommending that a review of spacers be considered.*

COMMENT Are the costs to the health system for implementing new recommendations being assessed?

Response: *The ODPRN is focused on the drug program and will not be assessing the costs associated with new recommendations or criteria.*

COMMENT Are the final recommendations made public?

Response: *Yes, final censored reports are released publically subsequent to the completion of each review. In order to maintain academic integrity and to avoid jeopardizing potential publications, final uncensored reports will be released 6 months subsequent to the completion of each review or upon publication.*

COMMENT We believe that recommendations regarding the reimbursement for this medication {for asthma} should be taken separately from decisions with respect to COPD, which is a different disease, with different contributing factors and a significantly different patient demographic. We would hope that, in Ontario, ICS+LABA, remain available on the ODB formulary as Limited Use for patients with asthma. We understand that patients without public or private coverage will continue to face accessibility problems.

Response: Our analysis found that ICS+LABA for asthma were efficacious and safe for patients with asthma, when compared to other long-acting agents. Since ICS+LABA combination products are used for both asthma and COPD with significant overlap in the patient population, and since it would be logistically unfeasible to list differently by indication in Ontario, we have made reimbursement recommendations for these products that would apply to both asthma and COPD indications.

COMMENT In our view, the ICS+LABA asthma class review document should have been finalized prior to the issuance of the Reimbursement Options for consultation. While the LAMA and ICS+LABA COPD class reviews have been finalized, the ICS+LABA asthma class review is currently “draft”. It is concerning that reimbursement options for ICS+LABA asthma are being evaluated when the corresponding class review is not yet final and the stakeholder consultation is not yet complete. We

consider the consultation to be a key component of the class review process that not only ensures transparency, but allows multiple stakeholders the ability to participate given the potential implications of policy changes for healthcare professionals and patients.

Response: *For our other completed drug class reviews (i.e., triptans, testosterone), the draft report and recommendations were presented concurrently. The respiratory drug class reviews were an exception due to the overlapping nature of the reviews (e.g., ICS+LABA for asthma and ICS+LABA for COPD).*

COMMENT A more transparent approach that includes the provision of detailed methodology would result in a more productive dialogue throughout the stakeholder consultation and a greater appreciation of the conclusions drawn. While we can appreciate the provision of detailed methodological information may impact publication, we do not believe this is a primary objective of the class reviews. A detailed understanding of the methods would facilitate richer stakeholder feedback throughout the consultation process. This would lead to a greater appreciation of the conclusions made in the class review documents, which is important given these conclusions are key considerations for the proposed reimbursement options.

Response: *The methodology for the review is outlined in detail in each of the research reports. Some of the uncensored results may not be posted for 6 months in full detail to allow for possible future publication.*

COMMENT Methodological limitations of the class reviews should be appropriately disclosed, and the document should include an appropriate disclaimer. The key considerations for each product class are derived from the two final COPD class reviews and the draft asthma class review. Based on the stakeholder feedback from the previous (COPD) and current (asthma) class review consultation process, we are concerned that strong conclusions were drawn from the respective class reviews and have informed the reimbursement options, with little acknowledgement of the limitations of the methodology of the respective class reviews. Minimally, the disclaimer included on the respective COPD class reviews should be applied to the ICS+LABA asthma and Reimbursement Options documents, and consideration given to expand the disclaimer to include other statements similar to those included in final CDEC recommendations issued by CADTH.

Response: *We currently have a statement in our "Acknowledgement/Disclaimer" 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 changes have been made.*

COMMENT We note that the clinical criteria proposed is largely consistent with that proposed by other HTA bodies (eg., CADTH). ODPRN may wish to consider how the clinical criteria, as assessed and established through the CADTH process, could be used as an input for class reviews.

Response: *The clinical criteria developed by CADTH and other organizations are taken into consideration in the development of clinical criteria for Limited Use and EAP listings.*

COMMENT ICS+LABA COPD, Efficacy: Please include reference to methodological limitations and more details of results. Similar to the feedback provided previously to ODPRN during the ICS+LABA COPD consultation, we believe the ranking analysis used to present the comparative efficacy profile of

the ICS+LABA products is not appropriate. ODPRN has acknowledged in response to stakeholder feedback that "*NNTs and NNHs are only used to help put the results into context.*" To complement the text, ODPRN should provide more details of results (eg. effect estimates and measure of variance such as ORs and 95% confidence intervals) to policy makers so that they can use NNTs and NNHs more appropriately. In addition, there are no randomized clinical trials which compared the efficacy of ICS/LABAs on the reduction of COPD exacerbations. We continue to question the findings when one of the products (MFC) stated as having among the highest probability of being the most effective for decreasing the risk of COPD exacerbations is not indicated for COPD, whereas Breo Ellipta is not listed in this category. *Breo Ellipta* is the only ICS+LABA which is specifically indicated for the reduction of exacerbations in COPD patients with a history of exacerbations, which speaks to the strength of the evidence available for *Breo Ellipta*. [*Breo Ellipta* PM, GSK 2014; Zenhale PM, Merck Canada Inc 2014].

Response: *Policy makers are provided with the full uncensored report and will have access to effect estimates, including 95% Credible Regions. It has been noted that there are no RCTs comparing the efficacy of the various ICS+LABA products with regards to the reduction of COPD exacerbations; however, using a network meta-analysis, we are able to look at comparative effectiveness of drugs that may or may not have been directly compared to each other. Although COPD is not a Health Canada approved indication for Zenhale, there have been several clinical trials that have studied this drug in patients for COPD. As well, the Pharmacoepidemiology analysis identified a cohort of patients with COPD (but not asthma) that are using Zenhale. The statement under ICS+LABA Key considerations for COPD has been amended: "…budesonide-formoterol combination (BFC) (number needed to treat NNT)=8) reduced exacerbations statistically significantly in patients with moderate COPD. It should be noted that the report states that: "MFC is not approved in Canada for treatment of COPD."*

COMMENT ICS+LABA COPD, Safety/Tolerability: Please remove confirmatory statements regarding the safety of fluticasone relative to other ICS or ICS/LABA. We continue to disagree with the suggestion that fluticasone is associated with a greater risk of pneumonia compared to budesonide. The totality of the data in COPD from both direct and indirect comparisons suggests that the incidence and risk of pneumonia for Advair and *Breo Ellipta* are comparable to other ICS+LABAs.

Response: *Based on the evidence from the Rapid Review team as well as the review of the observational studies, fluticasone propionate, alone or in combination with a LABA, appears to be associated with a greater risk of pneumonia than comparators. We caution that there are no head-to-head randomized controlled trials comparing BFC and FSC.*

COMMENT ICS+LABA COPD, Accessibility: We acknowledge that implementing Limited Use criteria for ICS+LABA for COPD may help guide therapy. This is particularly important to differentiate place in therapy from other respiratory product classes.

Response: *Thank you for your response.*

COMMENT ICS+LABA COPD, Pharmacoeconomics: Please include reference to methodological limitations. Further to the feedback provided to ODPRN with regard to the methodology of the *de novo* economic evaluation during the ICS+LABA COPD consultation, we question the findings that suggest that ICS+LABA are not cost-effective for patients with moderate COPD. We note that the Common Drug

Review (CDR) has issued a positive recommendation for *Breo Ellipta* for use in moderate to severe COPD (with clinical criteria), which included economic considerations [CADTH 2014].

Response: *In order to provide consistency across the ODPRN reports, the Pharmacoeconomic Team uses data from the NMA generated by the OPDRN Rapid Review Team. Although there are no RCTs that compared the efficacy of the currently available ICS+LABAs on the reduction of COPD exacerbations, the use of the network meta-analysis allows inferences into the comparative effectiveness of various interventions that may not have been evaluated against each other.*

COMMENT ICS+LABA Asthma, Efficacy: We believe that the quality of available data to assess the achievement of guideline defined control works best in favour of fixed dose vs. adjusted treatment approach for the following reasons. FSC is the only fixed ICS/LABA combination that has been prospectively studied and proven to achieve and maintain GINA/NIH defined control in The Gaining Optimal Asthma ControL (GOAL study) [Bateman, 2004]. In addition, 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]. This makes the generalisation of the SMART data toward clinical practice difficult.

Response: *The Rapid Review team looked at different dosage regimens as part of their NMA. Based on the results of their review, ICS+LABA at any dose (adjustable or fixed dose) was more effective in terms of decreasing exacerbations than other long-acting agents. Note that there is no discussion of "SMART" therapy in the Reimbursement Option report.*

COMMENT ICS+LABA Asthma, Pharmacoeconomics: Please revise this section to ensure consideration of clinical practice and the methodological limitations. Consistent with the feedback provided for the ICS+LABA asthma class review, we believe the *de novo* economic evaluation did not take into consideration all of the benefits of ICS/LABA combination therapy as well as the harms related to high dose ICS. In addition, a policy of not funding low to medium dose ICS+LABA combinations would contribute to further inappropriate use of high dose inhaled corticosteroids. This approach is inconsistent with Canadian and international treatment guidelines [Lougheed 2012, GINA 2014], which indicate that patients should titrate to the lowest effective dose. This approach could also lead to other healthcare related costs resulting from poorly controlled asthma and potential adverse effects for patients due to unnecessarily prolonged exposure to high dose ICS. Evidence of this is outlined in a review of Iceland's policy change that introduced a cost-saving approach to limit reimbursement for ICS+LABA. The analysis considered asthma and COPD and authors concluded that disease control was reduced, more OCS and SABA use was evident and more healthcare visits were recorded [Bjornsdottir et al 2014].

Response: *As stated in the introduction, the reimbursement option report summarizes information from each of the reviewed drug classes. It also provides a link for more detailed information (i.e., the full reports).*

- *Under the pharmacoeconomics section for ICS+LABA for COPD, we acknowledge that guidelines recommend use of ICS+LABA: "Although our analysis suggests that ICS+LABA products are not cost-effective for patients with moderate COPD, guidelines suggest use of these combination products in patients with moderate and severe COPD."*

- *Under the pharmacoeconomics section for ICS+LABA for asthma, a statement has been added: Note that guidelines recommend for patients 12 years of age and older who remain uncontrolled on low-dose ICS, the addition of a LABA, ideally in the form of a combination inhaler.*

COMMENT ICS+LABA Reimbursement Options, Option A [Exceptional Access Program (EAP)]: Given the volume of patients who benefit from treatment with ICS+LABAs in Ontario, we agree that it is not feasible to place these products in the Exceptional Access Program (EAP).

Response: *Thank you for your response.*

COMMENT ICS+LABA Reimbursement Options, Option B [Limited Use (LU)]: We note the proposed LU COPD criteria are similar to that recommended by CDR for *Breo Ellipta* in COPD [CADTH 2014]. Based on the current utility of ICS+LABA products in Ontario and the benefit/risk profile of all ICS+LABA products, the LU approach could help guide appropriate use and place in therapy, while avoiding the significant strain on the system mentioned by ODPRN in Option A. Please remove reference to *Advair* inhalation aerosol as it is not indicated for COPD; only Advair Diskus should be included in the list of medications to which the proposed LU criteria for COPD apply [ADVAIR PM, GSK 2014].

Response: *The clinical criteria developed by CADTH and other organizations are taken into consideration in the development of clinical criteria for Limited Use and EAP listings. Advair, but not Advair Diskus, has been removed as an option for LU listing for COPD.*

COMMENT ICS+LABA Reimbursement Options, Option C [General Benefit (GB)]: While this is a reasonable option, it may not address the utilization of ICS+LABA in patients who may not have a diagnosis of asthma or COPD which is stated as being as high as 20% of patients. Differentiation of place in therapy and/or appropriate use may not be achieved with this option.

Response: *Thank you for your response.*

COMMENT ICS+LABA Reimbursement Options, Option D [GB, Preferential List]: We encourage ODPRN to consider advances in therapeutic innovation together with potential implications to patient care and associated healthcare costs when evaluating options for medications covered by the Ontario Drug Benefit Programs. We believe the reimbursement option of GB where budesonide+formoterol (Symbicort) is preferentially listed over other ICS+LABA products for COPD does not align with the existing body of evidence, nor does it address the use of the asthma LU code in COPD. We disagree with the statement *"...evidence indicates that budesonide+formoterol (Symbicort) is most effective for decreasing risk of COPD exacerbations... compared to fluticasone+salmeterol (ADVAIR)"*. While keeping in mind the uncertainty of cross-study comparisons due to known and unknown variations across studies, it is relevant to note that the exacerbation reduction seen with FSC, BFC, and FVC versus their respective LABA, is comparable in similar patient populations (i.e., those with a history of COPD exacerbations). Further, we disagree with the statement "*...fluticasone, alone or in combination...is associated with greater risk for pneumonia..."* As mentioned in the comment above relating to Safety/Tolerability, the totality of the data in COPD from both direct and indirect comparisons suggests that the incidence and risk of pneumonia for *Advair* and *Breo Ellipta* are comparable to other ICS+LABAs. As ODPRN states, we agree this option could continue to result in physicians accessing other ICS+LABAs

for COPD using the asthma LU code. As well, it is important to keep all options available to physicians and patients since in most cases an individualized care plan is required.

Response: *Although there are no RCTs that compared the efficacy of the currently available ICS+LABAs on the reduction of COPD exacerbations, the use of the network meta-analysis allows inferences into the comparative efficacy of various interventions that may not have been evaluated against each other. Similarly, although there are no RCTs that compared the safety, especially in terms of pneumonia, of the currently available ICS+LABA products, the use of network meta-analysis allows inferences into the comparative safety of various interventions that may not have been evaluated against each other. We agree that preferential listing of Symbicort for COPD, may result in physicians accessing other ICS+LABAs for COPD using the asthma LU code. This is already noted in our report.*

COMMENT LAMA COPD, Efficacy: The primary role of bronchodilators should be clearly stated. Further to our comments provided during the consultation for the LAMA class review, we continue to believe that the endpoint of "exacerbations" does not align with the unmet need and appropriate place in therapy. While we acknowledge exacerbation data has been generated with bronchodilators, the primary role of LAMAs is to improve lung function and symptoms.

Response: *A statement has been added to the first paragraph of the Overview Section in the Reimbursement Option report: LABAs and LAMAs are inhaled bronchodilators and ICSs help to reduce airway inflammation.*

COMMENT LAMA COPD, Pharmacoeconomics: This section should include methodological limitations. Further to the feedback provided to ODPRN with regard to the methodology of the *de novo* economic evaluation during the consultation for the LAMA class review, we question the findings that suggest that LAMA medicines are not cost-effective for patients with moderate COPD. Other LAMA products, such as Seebri Breezehaler and Tudorza Genuair have been recommended by CDR and include economic considerations [CADTH 2013, CADTH 2014].

Response: *The pharmacoeconomic analysis analysis found that all LAMA monotherapies were cost effective compared to ICS single agents and salmeterol (Serevent) but not to formoterol (Oxeze) at the listed drug prices. The reimbursement option report did not provide any pharmacoeconomic analysis for LAMAs in patient with moderate COPD.*

COMMENT LAMA Reimbursement Options, Option A [Limited Use for all products]: We note one of the rationales for potentially transitioning LAMAs from General Benefit to Limited Use considers availability of data generated in patients with moderate to severe asthma. Anchoring this type of change in policy on the mere availability of data in other indications, particularly when current utilization data shows that these products are primarily used in the treatment of COPD, suggests that advancing scientific knowledge into a different therapeutic area can have unintended repercussions on patients and policy, and diminishes the value of therapeutic innovation. In addition, we note the LU criteria differs from that recommended by CADTH for *Seebri* and *Tudorza*, which includes listing similar to tiotropium or other LAMAs, with price a consideration for *Tudorza*. Therefore, it is not clear why the proposed clinical criteria for LAMA is limited to "moderate to severe COPD".

Response: *The option to move LAMAs as a Limited Use product is consistent with the restricted listing of these products in most jurisdictions across Canada (exception: Alberta, Ontario, Quebec). Clinical criteria (for Limited Use) may help to guide physicians to the appropriate prescribing of these medications for COPD. The Canadian COPD guidelines state that a long-acting bronchodilator can be offered to patients with more* persistent symptoms and moderate to severe airflow obstruction. The criteria have been amended to "Patient with COPD, persistent symptoms and moderate to severe airflow obstruction"

COMMENT LAMA Reimbursement Options, Option B [General Benefit (GB)]: Retaining the GB for LAMAs appears to be a reasonable option, given the current utilization data shows that these products are primarily used in the treatment of COPD.

Response: *Thank you for your comment.*

COMMENT Please correct "fluticasone" throughout the document. In the document, "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 document so that reference is made specifically to either FP or FF, as appropriate.

Response: *This has been amended throughout the Reimbursement Option report.*

COMMENT Please correct the conclusion of the document so that it aligns with earlier sections. The conclusion states that final recommendations for the funding of LAMA+LABA products will be made. This conclusion should be revised to refer to only "ICS+LABA and LAMA" products for consistency with the text on page 14 (*"...no recommendations for the listing of LAMA+LABA combinations products for OPDP will be made."*)

Response: *The conclusion has been updated to include the results of the Social Acceptability Research (i.e., Citizen's Panel) as well as feedback received from the stakeholders.*

COMMENT *Breo Ellipta* should state "Not Listed" for asthma in Appendix A (pg. 18). *Breo Ellipta* is presented in the table as being listed in the Ontario public plan as "Limited Use" in Asthma. Please note that *Breo Ellipta* is not currently indicated for the treatment of asthma and is not listed in Ontario [*Breo Ellipta* PM, GSK 2014].

Response: *Thank you for your comment; this has been corrected in the final report.*

COMMENT Please add date to table in Appendix A (pg. 18). In the event this document is consulted in future and the table no longer reflects current status, a footnote should be added to indicate the status of products is current "as of" a particular date.

Response: *A note has been added to the table to reflect when the table was compiled.*

COMMENT Consideration should be given to adding a Therapeutic Note stating that BFC (Symbicort) is approved for use as a controller and a reliever in asthma and may be of value in individuals 12 years of age and older, particularly exacerbation-prone individuals with

uncontrolled asthma despite high maintenance dose of ICS or ICS/LABA combination therapy.
Response: *No systematic review was undertaken for BFC as a controller and a reliever ("SMART" therapy). Although the Rapid Review team did consider adjustable and fixed dosage regimens in their NMA, no cost-effective analysis was completed for the different dosage regimens. Therefore, no recommendation for a Therapeutic Note will be made for BFC administered as a controller and a reliever in asthma.*

COMMENT Consideration should be given to adding a Therapeutic Note stating the LAMAs are not approved for use in asthma.
Response: *Although LAMAs are not currently indicated for the management of patients with asthma, recent evidence suggests that these medications may be helpful, especially in patients with uncontrolled moderate to severe asthma. Therefore, we will not recommend adding a Therapeutic Note as stated above.*

COMMENT Furthermore, the Qualitative Review notes that there is a perception of an over-reliance on ICS/LABA in primary care. This may be true, as many patients are started on combination therapy ICS/LABA rather than starting on ICS alone. This practice is contrary to the Canadian Thoracic Society Asthma Consensus Guidelines and other international guidelines, such as GINA, that support the step-wise approach. Therefore, we agree that LABA should only be added after a trial of ICS alone and we support the limited use code.
Response: *Thank you for your comment.*

COMMENT Our third recommendation is related to the use of spirometry for patients six years of age and older as the most effective procedure to support an objective diagnosis and management of respiratory disease.
Response: *Although we agree that spirometry is an effective diagnostic tool and is recommended in the Canadian COPD guidelines as well as the Canadian Asthma guidelines, we did not systematically review the evidence for spirometry in either disease. Therefore, no recommendations can be issued regarding spirometry in either asthma or COPD.*

COMMENT I agree with current reimbursement ie LU codes for combination products and full reimbursement for LAMA. I would be concerned if decision to use therapeutic substitution for class ICS/LABA based on price or pharmacoeconomics as there is clinically a huge variation in phenotypical symptoms of asthma (cough variant vs wheeze) and COPD (emphysema vs bronchitic) and response to each formulation.
Response: *Each option carefully considers all the evidence, including efficacy, safety, cost-effectiveness, clinical guidelines and patient/physician preference. One of the options considered for ICS+LABA is Limited Use (status quo for asthma and new code for COPD).*

COMMENT There are some patients who have an overlap syndrome of asthma and COPD (so

called ACOS) where the recommended initial therapy is an ICS/LABA. Limiting initial prescription to an ICS alone is likely to be detrimental for patient care.

Response: *Thank you for your comment. The focus of our ICS/LABA reviews was asthma and COPD; we did not review the evidence, including guidelines, for the overlap syndrome of asthma and COPD. However, your point will be taken into consideration in our final recommendations.*

COMMENT I feel strongly that low dose ICS/LABA should NOT have coverage removed. Doing so would have me practicing against the best published evidence based guidelines (GINA). There are many patients who cannot be controlled on low to moderate dose ICS who substantially improve when they are switched to ICS/LABA combinations. Once stabilized I would cut them to low dose ICS/LABA, always trying to find the lowest effective ICS dose). The benefits in those patients of low dose ICS/LABA therapy is superior than that achieved with low/medium ICS monotherapy and often as effective as, and certainly safer than, moderate to high dose ICS/LABA combination. Therefore, the reason for not funding low dose ICS/LABA totally escapes me. I will add that the most recent (2014) GINA guidelines suggest cutting the dose of ICS down as much as possible rather than eliminating the LABA component of the combination inhaler.

Response: *The discussion for not funding low dose ICS/LABA was presented in the cost-effectiveness model (as per Pharmacoeconomic Report). However, it should be noted that in the Draft Reimbursement Option report, this scenario was not considered a viable option.*

COMMENT The ODPRN presents 4 reimbursement options, with some supportive evidence and an economic analyses for each option. Based on the information presented, I would agree with the option ODPRN seems to propose (Option D), because it arguably provides the best cost-benefit and benefit/risk ratio.

a. BF being more efficacious than FS in reducing COPD exacerbations. However, direct evidence is not provided by ODPRN (reference 10 of the ODPRN document compared RCTs of individual drugs vs placebo) and to my knowledge there are no head to head RCTs comparing BF vs FS in COPD to support this argument.

b. Fluticasone has been reported to increase the risk of pneumonia compared to placebo, budesonide and LABAs. Indeed, the evidence supports the concept that in COPD, there is an increased risk of pneumonia with higher doses of inhaled corticosteroids (ICS) and the risk is higher for Fluticasone than for Budesonide and other ICS. I would make the same argument to favour BF over FS in Asthma, as there is emerging information suggesting that the risk of pneumonia in patients with Asthma is also increased with FS compared to the other ICSs and placebo(4); and there is no reason to think that the pathophysiologic mechanism through which FS increases the risk of pneumonia in COPD -and other ICS to a lesser degree- would differ in Asthma.

Response: *Thank you for your response. Option D (preferential listing) has been considered for ICS+LABA for COPD. As you noted, in our analysis, BF was considered more efficacious than FS in reducing COPD exacerbations. This was based on our NMA, which allowed inferences into the comparative effectiveness of various interventions that may not have been evaluated against*

each other. There are no head-to-head RCTs comparing the various ICS+LABA products. However, no comparison between Symbicort and Advair is available for the indication for asthma, and as such, we are not able to recommend preferential listing for asthma.

COMMENT Based on the information ODPRN presents, I would favour option B, because it would have apparently no impact on the current budget and provides alternatives that could improve for patients in clinically important outcomes such as lung function, dyspnea and exacerbations. I would also suggest analyzing the inclusion of Tiotropium for the management of patients with moderate to severe asthma Asthma that are not properly controlled with ICS/LABA, as there is evidence to support its use in this setting. In addition, we are currently using Tiotropium for these patients in clinical practice, which is likely cost-beneficial -by reducing hospital admissions-; however, it would be appropriate for ODPRN to do an economic analyses to better define this.

***Response**: Thank you for your response. Limited Use (Option 1) and General Benefit (Option 2) will be considered as options in our final recommendation. We agree that recent evidence has suggested that tiotropium, even though not indicated for asthma, may be helpful in patients with moderate to severe asthma. Allowing access to tiotropium via general benefit would enable use of this medication for these difficult to manage asthma patients.*

References

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