ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

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

LAMAs for COPD

Consolidated Report

December 19th, 2014

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COMMENT

There is an overall lack of transparency/details in the reports that affect our ability to comment on the appropriateness of the review. This is especially true with respect to the network meta-analysis and pharmacoeconomic reports. It should be noted that the relative risk of exacerbations have been censored in the report of the economic analysis. A request that these data be provided (to aid in the transparency and review) was denied. In addition, a previous request (March 2014) to see the "de novo" economic model was denied – thereby making it virtually impossible to comment on the accuracy and validity of the model itself.

Response: *Research conducted for drug class reviews is considered for peer-reviewed publication. However, full disclosure of the results on the ODPRN website for stakeholder review may prejudice future publication of the information in scientific journals. Therefore, some of the information in the reports is censored for a six-month period following completion of the review or until publication in a scientific journal.*

COMMENT

Given the significant (both stated and unstated) limitations to both the NMA and economic analysis, the recommendation "to list Seebri preferentially at currently listed drug prices, unless better prices can be negotiated for the other LAMA products" is not-supported. This recommendation incorrectly assumes that all LAMAs are interchangeable and does not take into account the costs to the healthcare system associated with implementation of such a recommendation.

Response: *It should be noted that the consolidated report on "LAMAs for COPD" does not make any final reimbursement strategy or policy recommendations. The economic analysis evaluated different scenarios, and based on the available evidence, concluded that glycopyrronium was cost effective when compared to aclidinium and tiotropium. Please note: an updated price for Tudorza has resulted in a revision in the conclusions reached by the Pharmacoeconomic team.*

COMMENT

Please consider updating exhibit 1 to include '*Restricted listing'* of Tudorza® Genuair® in all Provinces except AB, ON and QC (which have '*unrestricted listing'*). PEI is the only province where Tudorza® Genuair® is not listed yet.

Response: *Changes to Exhibit 1 have been made to update the available listing information of Tudorza.*

COMMENT

We recognize that the team has conducted a review about the side-effects of inhaled anticholinergics, particularly tiotropium bromide and ipratropium bromide on urinary retention among patients with COPD and the conclusions were reported in page 20 of the consolidated report. The section includes two observational studies that compared the risk of acute urinary retention (AUR) in COPD patients using tiotropium bromide and ipratropium bromide [Stephenson 2011; Afonso 2011]. Both studies showed comparable results. Notably, the study by Stephenson *et al* is particularly relevant since it is a population based case-control study using an administrative database for COPD patients in Ontario. Regarding this study, Almirall recommends that (i) the conclusion of the study be specific to the LAMA investigated (i.e. Tiotropium) and (ii) the relative risk of AUR be reported numerically. The **A**dsorption, **D**istribution, **M**etabolism and **E**xcretion (**ADME**) properties of the currently available LAMAs are not comparable and, thus generalization of the safety outcomes (e.g. systemic anticholinergic adverse events) to the current available inhaled anticholinergics is inappropriate. In addition, revising the reporting approach will accurately reflect the conclusion presented in the draft pharmacoepidemiology report (page 35) and ensure a consistent reporting format across the outcomes and type of studies (i.e. RCTs and observational) in the safety section of the consolidated report.

Response: *A sentence has been added under the "Observational Studies" to provide more detail on risk of acute urinary retention:*

A nested case-control study of individuals with COPD was conducted to determine the risk of acute urinary retention with short-acting (namely ipratropium) and long-acting (namely tiotropium) anticholinergics.(Stephenson 2011) The authors found that men recently initiating an inhaled anticholinergic had a 42% increased risk of acute urinary retention compared to non-users (odds ratio [OR], 95% CI 1.42, 1.20 to 1.68). No significant association was observed among women.

COMMENT

Furthermore, we advise the inclusion and discussion of a comprehensive systematic review evaluating the existing literature regarding the side effects of inhaled anticholinergics (i.e. tiotropium and ipratropium) especially on urinary retention among patients with COPD. In this review, Loke YK and Singh S [Loke 2013] included converging lines of evidence from a variety of data sources including case reports, observational studies, RCTs and pooled analyses of trial data. Importantly, the findings in this review are further strengthened by data presented in a poster format at ATS 2014. In this poster, Halpin *et al* [Halpin 2014], have provided an updated safety evaluation of Tiotropium using pooled data from 35 phase III and IV tiotropium clinical trials and underlined urinary retention (RR [95% CI]: 1.93 [1.21, 3.09]) and dysuria (RR [95% CI]: 2.16 [1.31, 3.57]) as two of the five most common anticholinergic adverse events in patients receiving tiotropium. It is important to recognize that randomized clinical trials often include participants at low risk for adverse events and, therefore the results are not always representative of clinical practice and generalizable to the overall population with COPD. In this case, clinical trials excluded participants at high risk for AUR such as those with symptomatic prostatic

hyperplasia or bladder neck obstruction and moderate to severe renal impairment. Consequently, results from these trials may, in fact, underestimate the risk of AUR in the *'real-world'* COPD patient. The dissemination of these findings coupled with the availability of new therapeutic approaches in the marketplace today may allow physicians to offer options with lower risks of these anticholinergics side-effects

Response: *The Pharmacoepidemiology Team only conducted a rapid review (not a full systematic review) of observational studies comparing LAMAs to other available therapies; as part of this review they included two relevant observational studies that assessed the risk of acute urinary retention in patients on LAMAs or SAMAs.*

COMMENT

In this regard, the two most recent available LAMAs, including Aclidinium Bromide and Umeclidinium Bromide, offer a unique advantage as no dose adjustment and no additional monitoring are required for COPD patients with renal insuffiency [Tudroza 2013; Incruse 2014]. This is in line with the current Canadian Spiriva® Product Monograph that tiotropium may be used in patients with moderate to severe renal impairment only if the expected benefit outweighs the potential risks [Spiriva 2012]. There should be additional precautions put in place for such high-risk patients that may include urological referral prior to initiating inhaled anticholinergics, or closer follow up and enquiry regarding any deterioration in urinary symptoms even before AUR occurs. Given the above, we strongly believe that appropriate recommendations on this topic are warranted in the consolidated report. Further rationale for inclusion of recommendations stems from the concerns voiced in letters to the editor of the TIOSPIR study where patients with moderate-to-severe renal impairment were excluded. In letters to the editor, Verhamme *et al* [Verhamme 2014] reported that concerns about increased mortality with tiotropium Respimat® seemed relevant primarily in patients with impaired renal function while Robert Wise, the first author of the TIOSPIR study, concluded that since tiotropium Handihaler® and tiotropium Respimat® have similar pharmacokinetic and pharmacodynamic properties, monitoring of adverse anticholinergic effects in patients with moderate and severe renal impairment is recommended regardless of the delivery device. In our view, recommendations regarding the use of tiotropium and glycopyrronium in patients with moderate and/or severe renal impairment should be reflected in the safety section of the consolidated report.

Response: *A summary of the use of LAMAs in patients with renal dysfunction, including a table outlining the similarities and differences between products, can be found in the Environmental Scan report. As none of the agents requires a dose adjustment or is contraindicated in patients with renal dysfunction (i.e., monitor patients or caution in patients with renal dysfunction), this information was not included in the consolidated report.*

COMMENT

In our opinion, the key considerations presented in the *safety and tolerability* section of the consolidated report do not fully reflect the data reported in the *safety and tolerability* section of this report (pages 18-20). Considerations regarding safety outcomes including cardiovascular-related mortality and AUR associated with tiotropium are missing in the consolidated report. Due to the serious nature of cardiovascular-related mortality and AUR on patient safety coupled with the significant increased risk of these side effects reported here with tiotropium we believe that it is important to describe this in the consolidated report.

Response: *Acute urinary retention was not an outcome from the RCTs that was abstracted by our systematic review team, although we did review the observational studies that assessed AUR in association with LAMA use. In addition, the observational studies that we reviewed only had data for tiotropium, and therefore it is unknown whether this adverse effect may occur with other LAMAs.*

With regards to the executive summary related to safety, the paragraph has been changed to:

"For the safety outcome of arrhythmias, no statistically significant differences were observed across any of the LAMA or LAMA+LABA comparisons. In contrast, LAMAs (i.e., glycopyrronium and tiotropium) decreased the risk of pneumonia compared with ICS+LABA. For the safety outcome of cardiovascular-related mortality, no significant differences were observed except for an increase in risk for patients treated with tiotropium when compared to LABA or ICS+LABA."

COMMENT

The Ontario Thoracic Society and the Lung Association have reviewed the Long-Acting Muscarinics for Chronic Obstructive Lung Disease Draft consolidated Report. We agree with the report, however we do have concerns related to one aspect of the draft report. Page 21 of the draft report contains the following statement: "Assuming that use of LAMA products is not expected to increase and that there is a willingness to continue to reimburse LAMA therapies, an optimal policy assuming a willingness to pay of $50,000 per QALY would be to list Seebri preferentially at currently listed drug prices, unless better prices can be negotiated for the other LAMA products." The Ontario Thoracic Society strongly believes that tiotropium (Spiriva) is by far the best-studied LAMA available, with multiple long-term RCT's (trials lasting from 1 to 4 years in duration) of thousands of COPD patients proving efficacy and safety. The same cannot be said for the other products. Switching millions of COPD patients to the cheaper alternatives might save a bit of money for the ODB drug budget, but would certainly necessitate extra patient visits to MD's to obtain new prescriptions, and in some cases, the medication switch could destabilize some patients. In contrast to Spiriva, the competitor LAMAs (Seebri and Tudorza) do not have long-term clinical trials proving safety and efficacy of their products, nor do they have data from long-term studies to prove that their products decrease the incidence of COPD exacerbation. Finally, importantly, there will also be patients who cannot tolerate Tiotropium and therefore, it is important to have all three options of LAMAs available to them.

Response: *It should be noted that the consolidated report on "LAMAs for COPD" does not make any final reimbursement strategy or policy recommendations. The economic analysis evaluated different scenarios, and based on the available evidence, concluded that glycopyrronium was cost effective when compared to aclidinium and tiotropium. Please note: an updated price for Tudorza has resulted in a revision in the conclusions reached by the Pharmacoeconomic team.*

A final report outlining reimbursement strategies/policy recommendations will be available upon completion of all three respiratory drug class reviews. Accessibility (including availability of alternative products) will be a key factor that will be taken into consideration in the development of the recommendations.

COMMENT

We would also like to ensure that the report is updated to reflect the recently released guidelines on "Prevention of Acute Exacerbations of Chronic Obstructive Pulmonary Disease: American College of CHEST Physicians and Canadian Thoracic Society Guidelines" (2014 http://journal.publications.chestnet.org/data/Journals/CHEST/0/chest.14-1676.pdf). The Guidelines clearly indicate that LAMAs should be used in patients with moderate to severe COPD to prevent moderate to severe acute exacerbations (with a level of Grade 1A evidence).

Response: *A summary of the LAMA recommendations from the recent guidelines has been included in the Environmental Scan Report.*

COMMENT

We also note that according to the Ontario Lung Association's 2011 report, *Life and Economic Burden of Lung Disease in Ontario*, if all people with moderate to severe COPD had access to pulmonary rehabilitation, the number of COPD-related visits to the emergency room would be reduced by 24 per cent, the number of hospital admissions would be reduced by 22 per cent and the length of costly hospital stays would shrink by 50 per cent. These reductions could provide Ontario's economy with gross savings of $76.2 billion over the next 30 years.

Response: *The focus of the drug class review report is drug therapy, in particular LAMAs for COPD. Under Treatment strategies (page 9), pulmonary rehabilitation is listed as a treatment strategy along with other management options such as smoking cession, drug therapy and educational programs.*

COMMENT

"For LAMA+LABA combination products, no statistically significant difference was noted for exacerbations in comparison to individual LAMAs, ICS+LABAs or LAMA+ICS+LABAs. The LAMA+LABA versus ICS+LABA and LAMA+LABA versus LAMA+ICS+LABA results should be interpreted with caution because only one trial provided direct evidence on each of these treatment comparisons."

Due to the important limitations of the systematic review (see section 2 of this document), the results should be interpreted with caution especially for the new LAMA/LABA fixed dose combination. As mentioned in the draft consolidated report, only one trial provided direct evidence comparing LAMA/LABA FDC versus ICS+LABA or versus LAMA+ICS+LABA in terms of exacerbations. In fact the available direct evidence comparing LAMA/LABA FDC versus LAMA with the exacerbation being a primary point is the SPARK trial where ULTIBRO BREEZHALER has demonstrated statistically significant reduction of moderate to severe exacerbation versus SEEBRI BREEZHALER. This would contradict the indirect comparison that has found no statistically significant difference in terms of exacerbations between LAMA/LABA combination products and individual LAMAs.

Response: *As stated in the consolidated report, the results of the LAMA+LABA comparisons should be interpreted with caution since only one trial provided direct evidence on each of these treatment comparisons. No changes have been made to the report.*

COMMENT

The main recommendations from both the ICS+LABA and from the LAMA draft reports have entirely focused on the pharmacoeconomic draft reports and specifically the BIA simulations. The qualitative and environmental drafts reports have provided some very insightful information. The patients have identified the quality of life as the most important outcome, followed by shortness of breath, and then by the functional abilities and mortality. In addition, and more importantly, the review of the appropriateness of prescribing for each drug class would have driven more crucial recommendations for the health outcome and indirectly for the spending's of the public drug plan. The inappropriate use of ICS in some COPD patients and in particular the fast switch from monotherapy to the triple therapy for patients in whom it's not recommended should have been addressed in this class review.

Response: *It should be noted that the consolidated report on "LAMAs for COPD" (as well as the previous "ICS+LABA for COPD") does not make any final reimbursement strategy or policy recommendations. A final report outlining reimbursement strategies/policy recommendations will be available upon completion of all three respiratory drug class reviews.*

A full review of the appropriateness of prescribing for ICS+LABA and LAMAs is beyond the scope of this review. The Environmental Scan reviewed and summarized Canadian and international guidelines for the management of patients with COPD, specifically related to use of LAMAs as monotherapy and triple therapy.

COMMENT

"Negotiating a 25% price reduction with both LAMA+LABA products would lead to an increase in expenditures". This recommendation is arbitrary and not well-founded as it appears from the analysis provided in this document given that the number of units used for the LAMA/LABA class were not appropriate. It was also shown herein that adjusting those assumptions will change drastically the results of the BIA (scenario GB18) for the LAMA/LABA from being costly (+$25.4M) to showing

substantial savings (-$6.9M) for the Ontario drug plan.

Response: *To address this comment, the pharmacoeconomic team included an additional sensitivity analysis. In the additional sensitivity analysis, analysis was based on assuming that users who switch from drug therapy including a LAMA product to LAMA/LABA products will use the same number of units previously consumed of LAMA products and that users who switch from ICS/LABA combination products to LAMA/LABA will use half the number of LAMA/LABA products than previous use of LABA/ICS products. This analysis found that funding LAMA/LABA combination products would lead to an increase in costs of less than 1% per annum. This is included in the report as a sensitivity analysis.*

COMMENT

Based on the underlying pathophysiology of COPD, bronchodilators aim to improve lung function and symptoms, whereas ICS/LABAs aim to reduce exacerbations and associated mortality risk in patients with a history of exacerbations (NICE 2010, GOLD 2014).

Response: *Although bronchodilators aim to improve lung function and symptoms, these agents have also been assessed for their ability to reduce exacerbation rates. The joint CTS/ACCP guidelines on prevention of COPD exacerbations evaluated the evidence for all inhaled therapy to prevent COPD exacerbations.*

COMMENT

Bronchodilators are the cornerstone of pharmacological management of COPD and current Canadian and international guidelines recommend their use as initial maintenance therapy in symptomatic patients with airflow limitation who are at low risk of exacerbations (GOLD 2014, CTS 2007).

Response: *As indicated in the consolidated report, bronchodilators are the foundation for treatment of patients with COPD. No changes have been made to the report.*

COMMENT

The Canadian Thoracic Society (CTS) and the American College of Chest Physicians (ACCP) jointly released new evidence-based guidelines for the prevention of COPD exacerbations (Criner et al 2014). Similar to the ODPRN, they considered the inclusion of novel agents (e.g. umeclidinium, vilanterol, aclidinium, glycopyrronium, and indacaterol), but the CTS/ACCP concluded that the information was too limited for an informed recommendation "...*to prioritize one type of therapy over another or make recommendations about combinations of therapy to prevent exacerbations*." (Criner et al 2014)

Response: *Although the new guidelines do not prioritize all of the treatment options, they do make a number of recommendations regarding comparisons of treatment regimens. For example in recommendation 14, in patients with moderate to severe COPD, the use of LAMA compared to LABA is recommended to prevent moderate to severe acute exacerbations of COPD. In recommendation 23, for*

patients with stable COPD, LAMA+LABA therapy OR LAMA monotherapy is recommended since both are effective to prevent acute exacerbations of COPD.

COMMENT

It was communicated at the ODPRN Workshop (28-Oct-2014) that reports for the LAMA and ICS/LABA COPD class reviews will be final in December 2014, with policy recommendations planned in February/March 2015, leaving a gap of 15 months between the cut-off date for evidence and the planned policy recommendation. GSK believes this will result in policy recommendations that are not founded on reasonably available scientific evidence. Further evidence for ANORO™ ELLIPTA® has been published since the data cut-off date

Response: *It is anticipated that policy recommendations for all three respiratory reviews (ICS+LABA for COPD, ICS+LABA for asthma and LAMA for COPD) will be available in February/March 2015. Policy recommendations will based on best available evidence at the time of the review(s).*

COMMENT

Of greater interest might be a network meta-analysis finalised in October 2014 conducted by MAPI which includes newer data and focuses on the endpoints identified during the qualitative work and required for regulatory approval (Huisman and Karabis 2014, Huisman et al 2014, Ismaila et al 2014).

Response: *The NMA conducted by MAPI that was finalized in October 2014 has not been published in a peer-reviewed journal, to our knowledge. Therefore we are unable to comment on this NMA.*

COMMENT

A stakeholder requests the complete body of relevant evidence for ANORO™ ELLIPTA® is considered, using relevant outcomes for the appropriate patient population, in order to make more accurate, informed, and timely policy recommendations. At the very least, GSK requests that ODPRN clearly states all of the methodological limitations of the review in accordance with internationally accepted standards of science, and that conclusions are limited to only those products and endpoints where the complete body of relevant evidence is considered to make a well informed and scientifically rigorous recommendation. In this case, the ODPRN should clearly indicate that important evidence for ANORO ELLIPTA was not assessed in its entirety, and indicate that reimbursement decisions for ANORO ELLIPTA be considered via the usual and well established national/provincial process.
RESPONSE: As this is a rapid review, an update of the literature search will not be performed at this time. If available at the time of publication of the final report, the Common Drug Review recommendations will be included.

Environmental Scan

COMMENT

Please consider updating exhibit 1 to include '*Restricted listing'* of Tudorza® Genuair® in all Provinces except AB, ON and QC (which have '*unrestricted listing*'). PEI is the only province where Tudorza® Genuair® is not listed yet.

Response: *Changes have been made to Exhibit 1 in Consolidated Report, and Exhibit 3 in Environmental Scan report.*

COMMENT

Dry Powder Inhaler (pages 28-29): As highlighted in this section, there are several factors that should be considered when selecting an inhaler device for COPD patients. In our view, proper use of the device with reduced margin of error is an important factor missing in this report. A key aspect of optimal COPD management is the patient's ability to master proper inhaler technique [Barrons 2011]. In this regard, studies have shown as many as 95% may not use their inhalers correctly [Souza 2009; Lavorini 2008]. Notably, inhaler misuse is associated with increased risk of hospitalization ($p=0.001$), emergency room visits ($p<0.001$), course of oral steroids ($p<0.001$) and antimicrobials ($p<0.001$) and poor disease control ($p<0.0001$) [Melani 2011]. As mentioned in this report, multi-dose DPIs including Genuair® and Diskus® are both easier to use and preferred by patients than single-dose DPIs (e.g. Handihaler) [van der Palen 2013; Anderson 2005]. This is in line with the association of Genuair® with fewer patient errors compared to Handihaler®; these include critical errors that impede delivery of sufficient dose or drug deposition in the lungs [van der Palen 2013]. Administration of effective therapies via a device that is simple to use and accepted by patients may help to improve treatment outcomes in patients with COPD [Anderson 2005; Chrystyn 2014]. Of note, inhaler errors have been shown to increase with age [Molimard 2008]. This is relevant since COPD is a disease predominantly in elderly patients who may have impaired vision, reduced manual dexterity and cognitive impairment. Furthermore, the objective of this report is aimed at patients supported by the Ontario Drug Benefit Program who are mainly elderly. Thus, easy-to-use devices that result in minimal margin of error should be considered when choosing a inhalation device and, thus we suggest that recommendation in this regard are made in this LAMA class review.

Response: *The aim of the rapid review of dry powder inhalers in the Environmental Scan report was to provide an overview of the various dry powder inhalers available. The report notes that several factors should be considered in the selection of a device including device/drug availability, patient age and ability to use device correctly, drug administration time and physician and patient preference.*

The Melani reference has been added to the report. "In an observational study that assessed the prevalence of inhaler technique in patients with COPD and asthma, older age ($p=0.008$), lower schooling ($p=0.001$) and lack of instruction on inhaler technique ($p<0.001$) were associated with inhaler misuse. As

well, inhaler misuse was associated with increased risk of hospitalization (p=001), emergency room visits (p<0.001), courses of oral steroids (p<0.001) and antimicrobials (p<0.001).”

COMMENT

Exhibit 13 (page 29): Please consider adding some clinically important attributes regarding the Genuair® device. Genuair® is a medium-airflow resistance device suitable for patients with a range of COPD severities. Importantly, the Genuair® inhaler is only pre-loaded multi-dose DPI inhaler in the LAMA class with multisensory feedback mechanisms (i.e. coloured control window and an audible click) to confirm successful dose inhalation.

Response: *Exhibit 13 has been updated to include the following statement for Genuair: “Feedback mechanisms (e.g., audible click, coloured control window) to confirm successful dose inhalation”*

COMMENT

We would also like to ensure that the report is updated to reflect the recently released guidelines on “Prevention of Acute Exacerbations of Chronic Obstructive Pulmonary Disease: American College of CHEST Physicians and Canadian Thoracic Society Guidelines” (2014 http://journal.publications.chestnet.org/data/Journals/CHEST/0/chest.14-1676.pdf). The Guidelines clearly indicate that LAMAs should be used in patients with moderate to severe COPD to prevent moderate to severe acute exacerbations (with a level of Grade 1A evidence).

Response: *A summary of the LAMA recommendations from the recent guidelines has been included in the Environmental Scan Report.*

Pharmacoeconomic Report

COMMENT

Of the 163 page report of this de novo model, only 8.25 pages were dedicated to describe the model structure, methodology, assumptions and source of data. A request for access to the actual model was refused. Exacerbations (especially those that result in emergency room visits or hospitalizations) are cost drivers in COPD and therefore are important components of the economic model (page 81; “… effectiveness was modelled in terms of the effects on exacerbation rates …”). The NMA derived relative risk of exacerbations were not included in the NMA report and were censored in the economic analysis report. A request to make these relative risks available was denied. This lack of detail makes it impossible to assess the validity of the model.

Response: *We accept that the redaction of data from the NMA limits the ability to review the data elements within the model. However, all other assumptions, study design features and data are presented in a transparent fashion such that the reader should be able to understand the methods used and how the data inputs were included in the model. We believe our model is valid in terms of*

reproducing the rate of exacerbations within community treated COPD patient.

COMMENT

Ipratropium bromide is incorrectly identified as a PDE-4 inhibitor (pages 19, 24, 27, 28), it is a short acting anticholinergic.

Response: *Thanks for pointing this out. We have made the appropriate changes.*

COMMENT

The price of aclidinium bromide reported in the economic analysis dated October 15, 2014 is incorrect, even though the correct price was published on the OPDP website on August 28, 2014.

Response: *We were provided a cost on August 25th based on wholesale prices. The report will be revised to address the price on the OPDP website.*

COMMENT

It is unknown what data (or the specifics thereof) from the NMA was used to inform the economic analysis. Whereas the NMA only reports selected information on moderate disease, the economic analysis includes severe and very severe disease (page 81: "… rather analysis assumed that treatment affected the rate of exacerbations with each state of disease severity with a resulting indirect effect on mortality. Data from the companion systemic review on the relative risk of all exacerbation across all disease severities were used within this analysis").

Response: *We accept that the redaction of data from the NMA does limit the ability to review that data element within the model.*

COMMENT

The 2nd paragraph on page 76 talks about mild, moderate and severe disease states whereas Figure 1 illustrates moderate, severe and very severe disease states

Response: *Thanks for pointing this out. The paragraph cited has been amended.*

COMMENT

The resource use components that are included in community based exacerbations are not defined. The cost cited in the model for community based exacerbations (Mittmann et al., Respir Med 2008) is NOT for "community" costs, rather, it reflects the cost associated with exacerbation related emergency room visits.

Response: *We used the cost from the Mittman article for moderate exacerbations as reported*

in Table 3. However, based on this comment we reviewed the paper and determined the methods in estimating this cost were faulty within the paper. We have revised the estimate to be the weighted average of the outpatient's costs and the emergency room visits costs. This comes to $198 rather than the reported $641. The reanalysis has been conducted using this figure and will make the incremental cost effectiveness ratios slightly higher.

COMMENT

The rate of total exacerbations in untreated patients was based on the placebo arm of the TORCH study. The stated rationale for using this datum was "patients within the placebo arm were not receiving either inhaled long acting beta agonists (LABA) (sic) or inhaled or oral corticosteroids and are therefore suitable for providing an estimate of the exacerbation rate in untreated patients". The assertion that this data appropriately estimates the exacerbation rate in untreated patients is false as the study protocol allowed use of other medications for COPD that have been shown to prevent exacerbations (e.g., ipratropium bromide) and the TORCH publications are silent with respect to what medications patients within the placebo group were actually taking. It would have been unethical to enroll patients in a multi-year study and prohibit use of COPD medications within the placebo arm.

Response: *It was difficult to identify rates of exacerbation by disease severity in an untreated population. We felt that the TORCH study was the best available source for data at the time of the review but if another more appropriate source was identified we would consider it within any further iteration of our work.*

COMMENT

It appears that the economic model has applied the same exacerbation rates across all disease severities. If this is indeed the case, it is incorrect. Multiple studies have shown that there is a significant increase in number of exacerbations as disease severity increases.

Response: *The comment is erroneous. As detailed in Appendix B1, exacerbation rates differ by disease severity in the model.*

COMMENT

Rather than using actual severe exacerbations/hospitalization data for the medications under investigation, the model used a derived value from indacaterol studies and apparently assumed that there was no difference in hospitalizations across medications. This assumption is not justified, nor is it supported by the data. In their assessment of the fixed dose combination of glycopyrronium and indacaterol vrs. glycopyronnium vrs. tiotropium, Wedzidcha and colleagues (Lancet Respir Med 2013) reported that patients in the glycopyrronium group experienced significantly more hospitalizations than the patients in the tiotropium group (RR = 1.43; 1.05 – 1.97, p = 0.025)

Response: *The comment does not effectively capture what was done in the economic model. Whilst we assumed that there were no differences in the proportion of exacerbations requiring hospitalization across treatments we did assume that the rate of exacerbations requiring hospitalization either decreased or increased by the relative risk associated with treatment. We would have gladly included differential relative risks by severity of exacerbations if this was consistently recorded across clinical trials.*

COMMENT

The reference for maintenance costs per year (excluding exacerbations), Table 6, is missing.

Response: *Thanks for pointing this out. The reference is in the text but has been added to the table.*

COMMENT

It would add clarity to indicate what was used as the measure of effectiveness in the Economic Evaluation. It is stated "In the analysis, effectiveness was modelled in terms of the effects on exacerbation rates which will have an indirect effect on mortality" (Pharmacoeconomic Unit, Treatment Effectiveness, page 81). If effectiveness is measured only in reduction in rate of exacerbations, then the full benefits of improved lung function, reduction in breathlessness, and improved quality of life is not accounted for in the evaluation.

Response: *As described in the report, in modelling the natural history of COPD, inclusion of multiple endpoints are liable to double counting of the mortality effect from disease progression. Analyses which incorporate multiple effects will involve double counting of treatment effects and bias in the estimates of cost effectiveness. We decided to adopt exacerbation rates as the outcome, based on the consistency of inclusion across RCTs and to follow previous economic models. It may have been feasible to include more outcomes if individual patient data from RCTs were provided.*

COMMENT

It would also be of benefit to confirm which list price was used for the products, as there were several inconsistencies in the Pharmacoeconomic Unit and the Environmental Scan and Local/Historical Context report.*

- *Pharmacoeconomic Unit, Appendix B1, Table 6 Data Estimates, the annual drug costs for Tudorza are indicated to be 28% higher than Seebri. This is questionable as both products have the same list price.
- Environmental Scan, Executive Summary states Seebri is listed at $53 and Tudorza is listed at $68, which is incorrect. Tudorza Genuair is currently listed at $53.10, matching Seebri. This is then accurately reflected in Exhibit 1: LAMA products available

in Canada. This should be updated for consistency throughout the document, including the Discussion section under Availability in Canada and Public Plan Listing in Ontario/Canada, and the Conclusion.

Response: *We were provided a cost on August 25th based on wholesale prices. The report will be revised to address the price on the OPDP website.*

COMMENT

In the Key Considerations section on page 23, under Efficacy, it is stated that "When LAMA products were compared with each other, no statistically significant differences were observed." If no differences in efficacy were observed, and the publicly listed price of Tudorza equals Seebri, then the question is raised how there could be such significant differences mentioned in the De novo Economic Evaluation when considering only the LAMA monotherapies. We request that this situation be clarified and revised to reflect the cost-effectiveness of Tudorza being the same as Seebri..

Response: *An economic evaluation is concerned with identifying the expected values of costs and outcomes. Thus the analysis is based on the expected values of input parameters and their uncertainty as represented by probability distributions. We have revised the report to include the published price of Turdoza.*

COMMENT

Please update the spelling of Tudorza throughout the Pharmacoeconomic Unit.

Response: *Thanks for pointing this out. Changes have been made.*

COMMENT

There is suggestion that upon review of the aggregate of scenarios leading to an increase in total COPD expenditure of 17%, it may be misleading to the reader. Specifically, not all scenarios are reasonable (e.g. 50% of at least moderate monotherapy LAMA or LABA users stepping up to LAMA/LABA), and therefore the requested price reduction may be exaggerated.

Response: *Our analyses were based on assumptions derived by clinical expert opinion. Should OPDP wish to consider other assumptions the analyses could be re-run.*

COMMENT

The analysis of the different assumptions reported and used in this BIA has revealed some important issues that severely compromise the findings and overall validity of the conclusions:

- Except for GB1 to GB3, the scenarios assume the same number of units for LAMA/LABA as for LABA or for ICS+LABA despite the products having different dosing regimens. The

revised assumptions for the units to use for the switches to the new LAMA/LABA and the rationale for the change are highlighted in the table 1 (see Appendix).

- Based on the above, the BIA has been calculated for the "at least moderate COPD patients" scenarios using the corrected number of units for LAMA/LABA (GB6, GB9, GB12, and GB15). The same exercise can also be done for the groups of severe or very severe. Given that the number of units used in the PE draft report (Appendix C1 page 134) has assumed the same number of units used for LAMA/LABA as for LABA, or for LABA/ICS, and that the corrected number is half the number used for LABA or ICS+LABA, therefore the cost of LAMA/LABA should be half the cost calculated in the PE draft report (Appendix C2 page 141) for the different scenarios (GB4 to GB15).The cost of LAMA/LABA has been corrected for the scenarios GB6, GB9, GB12, and GB15 in Tables 2 to 5 (see Appendix).
- Conclusion: The discrepancies observed between the assumptions used in the ODPRN draft BIA report and the revised assumptions based on the corrected number of units have demonstrated an important gap in the result of the BIA. Using the appropriate number of units result in significant savings ($6.9M) for the drug plan (Appendix, Table 6) if the LAMA/LABA FDC are listed on the ODB as a general benefit drugs.

Response: *To address this comment, we included an additional sensitivity analysis. In the additional sensitivity analysis, analysis was based on assuming that users who switch from drug therapy including a LAMA product to LAMA/LABA products will use the same number of units previously consumed of LAMA products and that users who switch from ICS/LABA combination products to LAMA/LABA will use half the number of LAMA/LABA products than prevous use of LABA/ICS products. This analysis found that funding LAMA/LABA combination products would lead to an increase in costs of less than 1% per annum. This is included in the report as a sensitivity analysis.*

COMMENT

The input parameters, serving as the basis for the model, do not represent real-world disease progression. Firstly, the parameters chosen were pooled from a multitude of subgroups (varying in sex, age, disease severity and exacerbation severity), each of which may have a large effect on the results. Secondly, there are a number of concerns with these parameters themselves, the primary one being equivalent risk of exacerbation across disease severities within a treatment. Furthermore, the model would have benefitted from acknowledging increasing severity of exacerbations and correlation between disease severity and treatment experience.

Response: *The inputs used in the model represent the best available evidence at the time of review. We did not assume the same risk of exacerbation by disease severity. We assumed that the risk of hospitalization with exacerbations increased with disease severity. We assumed mortality increased with disease severity indirectly due to the increased risk of exacerbation and the severity of*

exacerbations. As we wish our model to accurately represent the current clinical situation to ensure that it facilitates an evidence based policy making process, if better sources of real world disease progression were available we would happily include these in the model.

COMMENT

There is an important lack of reporting, especially with regard to input efficacy parameters such as the relative risk data of exacerbations that is omitted in Table 6 of Appendix B1 (PE draft report). Furthermore, the derivation for the calculation of number needed to treat or number needed to harm as presented in the report is based on odds ratios, whereas this report states using relative risks. The analysis would benefit from a presentation of odds ratios or relative risks, with estimates of dispersion. This represents a continuation of problems from the supporting NMA (see section 4).

Response: *We accept that the redaction of data form the NMA does limit the ability to review that data element within the model. Odds ratios from the NMA are converted to relative risks based on the baseline risk of event with no treatment.*

COMMENT

The model chosen may have been overly simplistic to represent treatment courses and their effect on COPD; there are many more variables that should have been taken into account. The model used relative risks of exacerbation based on treatment. It is stated that this method was used as opposed to including FEV1 parameters or increasing transition probabilities between disease states to avoid double counting of mortalities. However, it is possible to build a model that includes both these features and avoid double counting.

Response: *As described in the report, in modelling the natural history of COPD, inclusion of multiple endpoints are liable to double counting of the mortality effect from disease progression. Analyses which incorporate multiple effects will involve double counting of treatment effects and bias in the estimates of cost effectiveness. We decided to adopt exacerbation rates as the outcome based on the consistency of inclusion across RCTs and to follow previous economic models. It may have been feasible to include more outcomes if individual patient data from RCTs were provided. The inclusion of mortality data would require data from long term clinical trials measuring differences in mortality between treatments. To our knowledge this data does not exist. We therefore adopted an approach assuming that the reduction in exacerbation rates would correspond to a reduction in mortality, despite the limited evidence to support this effect of treatment.*

COMMENT

"Assuming a willingness to pay of $50,000 per QALY, it may not be cost effective to fund either LAMA+LABA combination product (Ultibro or Anoro Ellipta) if there is an inability to negotiate a price reduction. However, if a price reduction of at least 27% relative to its currently listed price can be

negotiated, reimbursement of Ultibro for patients with at least moderate disease would be optimal."

- The De-novo economic model results were derived from the systematic review. The use of the NMA results is considered a good practice; however the NMA from which these numbers have been derived may suffer from important limitations (described in the section 3 of this document). Therefore the conclusion that states that "if a price reduction of at least 27% relative to its currently listed price can be negotiated, reimbursement of Ultibro for patients with at least moderate disease would be optimal" is inappropriate and misleading.

- Although the draft report have identified many therapies as not being cost effective (LAMA not cost effective versus LABA, Spiriva and Tudorza not cost effective versus SEEBRI® BREEZHALER®, triple therapy not cost effective versus ICS + LABA), the sensitivity analysis has exclusively focused on the LAMA/LABA and the scenarios for price reduction targeted only LAMA/LABA. It should be noted that all these therapies that were not found cost effective in this model are currently reimbursed by the ODB.

- The objective of this class review being to modernize the public drug formulary and therefore all the options should have been looked at in the sensitivity analysis and in the BIA scenarios (whether LAMA is used as a monotherapy, in combination with LABA, or in triple therapy).

Response: *The focus of the class review is on LAMA related products. Thus, we conducted analyses which assisted in reaching conclusions with respect to LAMA monotherapies and LABA/LAMA combination products.*

COMMENT

" Negotiating a 25% price reduction with both LAMA+LABA products would lead to an increase in expenditures ($7.8 million or 5.2%)"

- The assumptions used in the BIA for the number of units used per day for the LAMA/LABA class needs to be changed as per Table 1 (see Appendix) in order to reflect the correct BIA scenarios (GB4 to GB15). Note that for the ICS+LABA class the units used per day1-11vary from 2 to 4 and therefore assuming ICS + LABA is used twice a day is a conservative assumption. Both the simulations of general benefit status for the LAMA/LABA and the need to reduce the price by 25% are arbitrary and misleading due to the use of inappropriate assumptions for the new drug scenarios. By correcting the number of units, the revised BIA (see Appendix, Table 2 to Table 6) results in significant savings for the ODB. In addition, the combination therapies such as Advair, Symbicort, or Zenhale are listed on the ODB as limited use (LU); therefore it's more likely to expect a limited use benefit status for the LAMA/LABA FDC and not a general benefit status. In light of this, scenarios GB1-GB3 that assume the use of LAMA/LABA as a first line

medication would have not been included in this analysis, and this would have increased further the savings links to the LAMA/LABA.

Response: *To address this comment, we included an additional sensitivity analysis. In the additional sensitivity analysis, analysis was based on assuming that users who switch from drug therapy including a LAMA product to LAMA/LABA products will use the same number of units previously consumed of LAMA products and that users who switch from ICS/LABA combination products to LAMA/LABA will use half the number of LAMA/LABA products than previous use of LABA/ICS products. This analysis found that funding LAMA/LABA combination products would lead to an increase in costs of less than 1% per annum. This is included in the report as a sensitivity analysis.*

COMMENT

"The reimbursement based economic evaluation found that for LAMA/LABA combinations, it is optimal (cost saving and cost effective) to reimburse indacaterol/glycopyrronium (Ultibro) if decision makers can negotiate a price reduction of at least 27%. Under no price reduction scenario would it be worthwhile to reimburse umeclidinium/vilanterol (Anoro Ellipta). With respect to LAMA products, it is optimal to list only glycopyrronium (Seebri)." Company A believes that the pharmacoeconomic evaluation is not valid and should not be the basis to inform policy; the conclusions drawn from the pharmacoeconomic evaluation are not appropriate.

Response: *We disagree. The intention of our analysis is to derive models which accurately represent the current clinical situation to ensure that it facilitates an evidence based policy making process. There is no intended bias in our analysis and if better sources of real world disease progression were available we would happily include these in the model.*

COMMENT

The *de novo* economic evaluation uses the efficacy and safety data synthesized from the Systematic Review Unit which included drugs that were recently approved by Health Canada. However, not all of the data that was used to support the regulatory submission were included in the systematic review. As such, it would be most appropriate to refrain from drawing conclusions in the absence of a complete analysis since it is likely that including all of the key data could impact the resulting recommendations.

Response: *We used data from the systematic review which included only published data subject to peer review. Once further such data becomes available, OPDP can decide whether further analysis is justified. We will happily go along with their wishes.*

COMMENT

The *de novo* economic evaluation ought to account for all clinical outcomes relevant to the various disease phenotypes and severities, not just exacerbations and mortality.

Response: *If manufacturers reported their clinical trials in such a detailed fashion we would gladly*

report results of a stratified analysis. However, we are limited due to the lack of data available.

COMMENT

The *de novo* economic evaluation does not appear to account for important treatment benefits and costs that may be differentiated between interventions. As ODPRN states in its report, *"[i]ncorporating the effect of treatment on FEV1 can lead to both an improvement in COPD severity and a delay in transitions across disease severity and thus, [has] an indirect effect on both exacerbation rates and mortality*" (ODPRN LAMA Class Review, PE Report, page 81). A majority of trials studying the effect of interventions on COPD have used FEV1 as a primary endpoint (Jones et al 2012, Kerwin et al 2012, D'Urzo et al 2011, Donohue 2013, Decramer 2014). ODPRN's decision to include only exacerbation effects and to fix FEV1 effects across all interventions limits the discriminative value of the model.

Response: *As described in the report, in modelling the natural history of COPD, inclusion of multiple endpoints are liable to double counting of the mortality effect from disease progression. Analyses which incorporate multiple effects will involve double counting of treatment effects and bias in the estimates of cost effectiveness. We decided to adopt exacerbation rates as the outcome based on the consistency of inclusion across RCTs and to follow previous economic models (e.g. Chuck et al. 2008). The difficulty with respect to FEV1 as an outcome is the lack of long term data demonstrating a consistency of treatment effect. Any economic analysis based on this outcome would need to adopt either short term time horizon or a degree to waning of treatment effect.*

COMMENT

Disease progression is associated with a number of modifiable variables such as lung function, quality of life, and exercise tolerability, dyspnea, and exacerbations (Pauwels et al 2004, O'Donnell et al 2007, GOLD 2014, Hurst et al 2010, Calverley et al 2007). In clinical trials the differential effects of therapies on these variables are directly compared. It is recommended that in addition to exacerbation and mortality, COPD treatment modifiable outcomes be accounted for in the evaluation, including lung function, quality of life, exercise tolerability, and dyspnea.

Response: *We agree that the fundamental outcomes of importance to patients are quality of life and mortality. The duration of clinical trials in COPD do not facilitate focus on the latter outcome. The failure to report the results of the impact of treatment on QoL in COPD trials could be addressed as, in many instances, such data were collected. In the majority of cases, however, these data have not been made available. A model focusing on treatment impacts on QoL and survival would be optimal if such data were available.*

COMMENT

Approximately 70% of COPD patients have an average of less than one exacerbation per year (Haughney et al 2014). Furthermore, the majority of these patients remain as infrequent exacerbators in the subsequent years (Hurst et al 2010). As such, a majority of patients with COPD are at low risk of

exacerbation yet require bronchodilator therapy to manage their disease. Since the majority of patients with COPD are at low risk of exacerbation yet require bronchodilator therapy to manage their disease, a more suitable model would incorporate the effects of lung function on disease progression and severity (please refer to Appendix 2).

Response: *The difficulty with respect to FEV1 as an outcome is the lack of long term data demonstrating a consistency of treatment effect. Any economic analysis based on this outcome would need to adopt either short term time horizon or a degree to waning of treatment effect.*

Systematic Review Team

COMMENT

The methods section, as written, does not provide sufficient detail regarding study inclusion and exclusion criteria.

- While included in Appendix 6, reference # 181 (Wedzidcha et al, Lancet Respir Med 2013) does not appear in Appendix 7. It is not clear if the exacerbation data from this study was included in the analysis. Given that it is one of the only head to head studies of LAMAs that evaluated exacerbations, if this study was not included, the rationale for exclusion should be detailed.

Response: *Wedzidcha et al (2013) was identified through scanning the reference lists of included studies. We were unable to include this study in our original exacerbations analysis, since this is a rapid review and this step was not completed for the ODPRN deadline, due to a lack of time and resources. However, we were able to include this study in some of our other outcomes.*

COMMENT

What the network looks like (show illustration).

Response: *We will not be sharing the network diagrams at this time.*

COMMENT

The specific methodology used in the NMA to control for sources of heterogeneity across studies has not been described. It is uncertain if the NMA actually controlled for:

- Differences in concomitant therapy (in both active and "placebo" arms). Differences in background therapy can have a significant impact on the effect size reported in published studies and therefore on the relative effect size across different compounds. The draft report does not describe if or how the NMA controlled for differences in background therapy.

- Differences in patient populations (e.g., exacerbators versus non-exacerbators). Differences in patient populations can significantly impact on the effect size reported in published studies and therefore on the relative effect size across different compounds.

- Heterogeneity in baseline prognostic factors has not been addressed in the analyses: this draft report lacks reporting on specific baseline characteristics of the included trials. This data is consolidated into one paragraph on page 7 of the draft report, and only ranges are provided (year of publication, number of patients per trial, duration of long-acting inhaled agents, age and percent female). There is no appendix documenting trial baseline characteristics, nor is this mentioned in the limitations section of the discussion. To maintain validity of the NMA, specific principals must be satisfied with regards to homogeneity between studies.(Dias 2011; Jansen 2013) These involve assessing inclusion of studies into analyses based on baseline characteristics, which were not done in the current NMA.(Dias 2011; Jansen 2013) It has been previously demonstrated that these factors play a significant role in disease progression and controlling for these covariates produces more valid estimates.(Jansen 2014b)

- Duration of treatment across trials suffered from considerable heterogeneity and is poorly reported: It is stated on page 7 of the report that the "…duration of treatment with long-acting inhaled agents ranged from 9 hours to almost 4 years." There were two ways to account for these differences: either by incorporating trial duration into the statistical model (e.g., meta-regression) or by grouping studies of similar length together and presenting the results separately as a sensitivity analysis. Neither of these strategies was employed. These differences may compromise the validity of the primary outcome analyses.

- The ODPRN review included peer-reviewed studies regardless of their duration, patient population (including disease severity and history of exacerbations), and definition of exacerbation; this suggests a significant risk of bias in the analysis:

    - Many studies were generally too short in duration to adequately measure these endpoints.

    - Clinical trials have used widely different methods to define and analyse COPD exacerbations and this can lead to biased estimates of treatment effects (Aaron et al 2008).

    - Some study enrollment criteria required patients to have a history of exacerbations or were more severe patients making the signal of exacerbation stronger.

    - These sources of potential heterogeneity should have been explored via sensitivity analysis and meta-regression to assess the robustness of the

presented results. It would be particularly interesting to use sensitivity analyses to evaluate whether limiting the analysis to those studies which were identified as being low risk of bias changed the results.

Response: *Since this is a rapid review, we were unable to conduct subgroup analyses due to time constraints.*

COMMENT

The March 3, 2014 comprehensive research plan identified hospitalizations (all cause and due to exacerbations) and number of emergency room visits (all cause and due to exacerbations) as outcomes of interest. No explanation was provided as to why these outcomes were not reported. As emergency room visits and hospitalizations are the primary cost drivers in COPD, it is important that these outcomes be assessed and reported.

Response: *As described under the methods section, we selected 5 outcomes for analysis based on feedback from our stakeholders.*

COMMENT

The NMA focusses on moderate disease severity and then generalizes the results – this is not appropriate. While a NMA may not have been possible for all disease severities, other methods should have been explored and results reported.

Response: *A network meta-analysis was first done for all severities; in cases where inconsistency between direct and indirect evidence was present statistically, we presented sub-group analysis by disease severity. We then considered conducting pairwise comparison meta-analysis. If there was insufficient data to complete a network meta-analysis or meta-analysis, a description of the results was provided in the text (e.g., for severe exacerbations).*

COMMENT

Please see Suissa Thorax 2013 regarding the correct method of calculating NNT for COPD exacerbations and pneumonia.

Response: *Thank you for pointing out this most interesting paper. However, we did not use the relative risk or risk difference to calculate the NNT/NNH. Instead, we used the method proposed by the Cochrane Handbook (available at http://handbook.cochrane.org/), which is to use the formula using the odds ratio. We prefer to use this method for the NNT/NNH, as the one proposed in the paper has not been formally validated.*

COMMENT

As for the definitions of the outcomes, appendix 7 of the draft report looks at varying definitions of the

primary outcome of interest: exacerbations. Patients can range from mild to very severe exacerbations, the definitions of each varying between included studies. Of the 92 studies included in the analysis for the primary outcome, 27 do not define the outcome. The remaining studies' definitions varied, the most common definitions referring to a change in treatment (30 studies) or symptom worsening for more than two or three days (15 studies), depending on the study. These inconsistencies were accounted for by a separate analysis looking only at moderate exacerbations. The only other outcome for which the spectrum of definitions is described (Appendix 8), pneumonia, varies considerably with only 14 of the 33 trials included in the analysis reporting any definition. These differences were not accounted for in the analysis presented. A complete analysis would have looked at possible effects of these varying definitions through a sensitivity analysis.

Response: *This is a rapid review. We were unable to perform subgroup analyses due to time constraints.*

COMMENT

There is a significant lack of reporting with regards to details of the statistical methods. One major piece of information needed to assess the validity of the model is whether the analysis was conducted in either a Bayesian or frequentist framework. This can have major implications on the interpretation of results as well. If a Bayesian framework is used, many more details are required to assess the validity of the models. No information pertaining to this is reported. It is also stated that a random-effects model was used (Draft of the Systematic Review report, page 6, parag. 3). However, details were not reported. There are multiple ways to apply a random-effects approach and thus, results can vary with regard to precision and reliability.

Response: *A frequentist approach was used. We have clarified this in the methods section.*

COMMENT

Atypical reporting of results renders them uninterpretable to most audiences. Comparisons were reported in two ways; either qualitatively, with a statement as to the superiority of one class over another, or in the form of number needed to treat (NNT) or number needed to harm (NNH). Neither of these reporting formats provides direct comparative estimates or uncertainty intervals (either confidence intervals or credibility intervals), which compromises the findings of the analyses as well as readers ability to interpret findings. ISPOR good reporting standards suggest reporting results as either odds ratios (ORs) or relative risks (RRs).(Jansen 2014b) Lack of reporting on these measures compromises the applicability of this report.

Response: *While we agree, we are unable to report ORs or RRs in this report so that we can publish our results. This is consistent with the other NMA teams who are part of the ODPRN.*

COMMENT

The clinical evaluation is based on an assessment of COPD exacerbations and mortality; these endpoints do not align with the primary role of bronchodilators in the management of COPD and do not reflect the unmet need in the patient population for bronchodilator therapy.

- In selecting endpoints that are better suited to an ICS/LABA, ODPRN has relied on analyses from clinical trials of which the overwhelming majority were neither designed nor powered to assess these two outcomes. The only study powered on exacerbations for a LAMA/LABA fixed dose combination was enriched with severe to very severe COPD patients who had a history of ≥1exacerbation. 75% of the enrolled patient population used concomitant ICS. Any difference in exacerbation rate between the LAMA/LABA and LAMA component occurred in patients on background ICS (Wedzicha 2013). This trial demonstrates patients at risk of exacerbations significantly benefit from ICS in combination with one or two bronchodilators on the reduction in the rate of moderate-to-severe exacerbations.

- Mortality is not an efficacy endpoint used in phase 3 clinical trials for respiratory medicines, and no bronchodilator has ever been shown to be associated with mortality benefits in COPD. Any mortality benefit, if it exists, has been observed in a post-hoc analysis in a sub-group of patients in the presence of ICS (UPLIFT trial; Tashkin 2008).

- Most of the studies included in this analysis were not specifically designed to look at exacerbations or survival.

- Selected efficacy outcomes should be matched to the treatment effect and goals of a given therapy. Most clinical trials in COPD include FEV1, the principal measure of lung function, as a primary outcome. The value of this endpoint has been recognized by patients, regulators and formulary bodies. The COPD research community and regulatory agencies (e.g. FDA, EMA) have identified FEV1 as an objective and repeatable index of airflow obstruction that has the capacity to measure symptomatic relief and disease progression in patients with COPD (Cazolla et al 2008, FDA 2007, EMA 2012). The significance of FEV1 in COPD is reflected by national and international bodies such as the Canadian Thoracic Society (CTS), GOLD, the American Thoracic Society (ATS) and the European Respiratory Society (ERS), and each promote the use of FEV1 as a means of defining and staging COPD (CTS 2007, GOLD 2014, Celli 2004).

- The findings of the qualitative research report suggest that functional improvement and health status are most important to patients and physicians alike. Despite these endpoints being identified as the most valuable, the Systematic Review and Pharmacoeconomic Review Units chose other endpoints (COPD exacerbations and mortality).

- Until the availability of the dual bronchodilator inhalers such as ANORO™ ELLIPTA®, the use of dual long-acting bronchodilation via separate products was limited and many patients likely progressed to the addition of an ICS/LABA combination for symptom management. This likely resulted in early utilization of ICS in these patients, who would be more optimally treated with additional bronchodilator therapy.

Response: *The set of efficacy and safety outcomes included in our analysis were selected in consultation with our stakeholders. Further, we wanted to avoid overlap with a recent Cochrane review and network meta-analysis that compared ICS, LABA, ICS/LABA combination and LAMA, on mean FEV1 and quality of life.*

COMMENT

The draft class review has included dual bronchodilator products (i.e., LAMA/LABA combination products such as ANORO™ ELLIPTA®), but does not consider the entire body of evidence available. The cut off-dates selected for the evidence will result in a class review that will be outdated at the time of the policy recommendation.

- Newer medicines (e.g. ANORO™ ELLIPTA®) included in the report had limited published data at the time of the data cut-off chosen for the report and continue to be evaluated via the Common Drug Review process. Unfortunately, the information sources utilized and the mid-November 2013 cut-off timeframe of the literature search have resulted in an incomplete data synthesis and inappropriate conclusions.

- We note that the search methodology focused solely on peer reviewed manuscripts, and therefore information available on clinical trials.gov and other publicly available information (e.g. conference abstracts/posters, company clinical trial registers) were not considered.

- Only one clinical study for ANORO™ ELLIPTA® (Donohue, 2013) has been considered in the class review, despite the availability of data from the extensive global clinical development program comprising seven Phase IIIa studies that has supported regulatory approval in 42 countries. The exclusion of these data from the review introduces bias in favour of established therapies and ignores advances in therapeutic innovation.

- The rationale to make a decision on inclusion of data from medicines that are not yet available is not clear (tiotropium/formoterol combination, GSK961081), particularly when relevant data for drugs which are available (eg., ANORO™ ELLIPTA®) have been excluded, and which the ODPRN should consider to be directly applicable to the class review. This further reinforces the position that the data sources and the cut-off dates for this class review will result in policy recommendations that do not reflect all of the

relevant available evidence.

Response: *This is a rapid review. An update of the literature search will not be performed at this time.*

COMMENT

The use of ranking analysis to compare the efficacy and safety profile of products is not appropriate for clinical decision making. As confirmed in previous correspondence, ODPRN indicated that the ranking of treatments is based solely on the magnitude of effect size and does not depend on clinical relevance or statistically significant results. According to the Cochrane Comparing Multiple Interventions Methods Group, "*Ranking measures are not an alternative to treatment effects! They cannot be interpreted clinically*." (CCMIMG, 2013). We therefore believe that this ranking analysis cannot be used to support the conclusions related to clinical efficacy and safety of inhaled therapies for COPD.

Response: *The ranking is not meant as an alternative to treatment effects. Rankings must be interpreted alongside clinical relevance and statistically significant results.*