ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

FINAL REPORT

Inhaled corticosteroids in combination with long-acting beta$_2$-agonist (ICS+LABA) for chronic obstructive pulmonary disease (COPD)

Pharmacoeconomic Unit

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Note

Some details are censored in this report so as not to preclude publication. Publications (when available) or final unpublished reports will be available on the ODPRN website (www.odprn.ca)

Executive Briefing

- This report assesses the current evidence for the cost-effectiveness of ICS in combination with LABA for chronic treatment of chronic obstructive pulmonary disease and the economic impact of alternative changes to the funding status of chronic obstructive pulmonary disease.

- Studies identified in the systematic review of economic evidence have contradictory results and the quality and relevance of these studies limit their applicability to this study's questions.

- In 2012, COPD expenditure by OPDP was $141.6 million.

- If triple therapy (involving a single inhaler for both ICS and LABA with LAMA (dual) and dual therapy (single inhalers for ICS and LABA) users moved to a combination product (ICS+LABA), there would be a small absolute reduction in expenditure by OPDP.

- For patients receiving ICS and LABA via separate inhalers, this analysis supports the cost effectiveness of moving to administration of the combination via a single inhaler. The incremental cost per QALY gained for ICS and LABA combination therapy when compared with LABA alone ranged from $80,000 to $260,000 dependent on the severity of disease. The incremental cost per QALY gained for triple therapy with ICS+LABA combination in addition to LAMA compared with LAMA alone ranged from $85,000 to $160,000 dependent on the severity of disease.

Executive Summary

Research Questions

RQ1 What is the current evidence for the cost-effectiveness of ICS in combination with LABA (ICS+LABA) for chronic treatment of chronic obstructive pulmonary disease (COPD) compared to single or combination therapies incorporating long-acting beta$_2$-agonist (LABA), long-acting anticholinergic (LAMA) and inhaled corticosteroids (ICS)?

RQ2 Based on a de novo economic model, what is the cost-effectiveness of ICS+LABA for chronic treatment of COPD compared to single and combination therapies incorporating LABA, LAMA and ICS?

RQ3 What is the economic impact of alternative policies for reimbursing ICS+LABA for chronic treatment of COPD?

Methods

Systematic Review of Published Economic Evaluations

To address RQ1, we conducted a systematic review of the available literature on the cost-effectiveness of ICS+LABA for treatment of COPD compared to: single or combination therapies incorporating LABA, LAMA and ICS. The focus of the systematic critical review was on the strength and quality of evidence addressing the cost-effectiveness of ICS+LABA. The generalizability of the studies to Ontario Public Drug Plan (OPDP) was based on whether the study adopted a Canadian perspective, modelled distinct COPD severity populations, modelled a lifetime time frame, and reported incremental cost-effectiveness ratios.

De novo Economic Evaluation

To address RQ2, an independent de novo economic model was developed to assess the cost effectiveness of alternative reimbursement strategies for ICS in combination with LABA compared the current strategy. A Markov model was developed which modelled disease progression combined with rates of exacerbations and death. Natural history data relating to disease progression was combined with treatment effectiveness and adverse event data from the clinical review conducted as part of this class review. Costs and utilities associated with disease severity, treatment related adverse events and exacerbations were derived from the literature. Analysis was conducted from the perspective of the Ministry of Health with results presented as incremental cost per quality adjusted life years gained. Detailed deterministic and probabilistic sensitivity analysis was performed to determine decision uncertainty. Results were stratified by severity as defined according to GOLD guideline criteria for COPD diagnosis.[1]

Reimbursement Based Economic Assessment

To address RQ3, an applied, policy-oriented economic model was developed to facilitate the reimbursement decision. Afterwards, alternative approaches to reimbursement of COPD therapy were identified. Strategies were identified during the scoping assessment along with further consultation with OPDP. The final step involved forecasting the budget expenditure on COPD treatments for each alternative reimbursement strategy.

Findings

Systematic Review of Published Economic Evaluations

A comprehensive search of the literature identified nine studies: five studies considered monotherapy, dual therapy and placebo/no therapy, two studies considered monotherapy versus dual therapy, while one report considered monotherapy, dual therapy and triple therapy, and another considered monotherapy, dual therapy and triple therapy along with combinations including a phosphodiesterase type 4 inhibitor (PDE-4) – roflumilast. In general, the literature examining the cost effectiveness of ICS+LABA contained a number of common limitations, including choice of assumptions and potential for bias in manufacturer-sponsored studies. This significantly reduces its usefulness in aiding in decision making.

Only one Canadian study was found.[2] Its results suggest that ICS+LABA was more cost effective than LABA in patients with Stage 3 COPD (based on the American Thoracic Society criteria), though its cost effectiveness in patients with Stage 1 and Stage 2 was unclear. Despite the strengths, this study had limitations primarily related to potential for bias related to study sponsorship.

Only two studies, the studies conducted by National Clinical Guideline Centre (NCGC)[3] and Oba[4] , were independent of manufacturer sponsorship. Both studies compared ICS+LABA to a variety of comparators. The population modelled in the analysis by NCGC was patients with severe to very severe COPD with a mean age of 66, while patients with moderate to very severe COPD with a mean age of 65 were modelled in the analysis by Oba. In both studies, time horizon was limited to three and four years.

The NCGC report reached divergent conclusions depending on the source of effectiveness data which limits its usefulness in decision making. The study by Oba which evaluated the cost effectiveness of ICS+LABA compared to monotherapies (LABA or ICS) and placebo only used effectiveness data derived from a single randomized controlled trial and the lack of transparency in reporting questions its applicability. The incremental cost effectiveness ratio for ICS+LABA versus placebo/no therapy was $52,046/QALY.

The further seven studies (including the one Canadian study) were manufactured sponsored; the results of all of these favoured the manufacturer's treatment where study inputs potentially biased results in favour of treatment.

Given the contradictory results from the manufacturer sponsored studies and the independent studies and the consistent concerns over the quality and the relevance of the available studies, it is not possible to make any inferences on which if any patient population the use of ICS+LABA is cost effective.

As a result, to assist with the ODPRN review, an independent de novo economic model was conducted to address the cost effectiveness of alternative reimbursement strategies for ICS in combination with LABA compared the current strategy.

De novo Economic Evaluation

Based on the lack of evidence from the systematic review, it was assumed that there is no difference in efficacy or adverse events between administration of an ICS and LABA via a single inhaler and administration via two separate inhalers, thus a cost minimization analysis was conducted. In the case of both the budesonide+formoterol combination and the fluticasone+salmeterol combination, the cost of the single inhaler combination product is lower than the cost of receiving the two medications via separate inhalers, suggesting that a move from dual therapy to combination therapy will be cost effective.

In all severities of COPD, ICS+LABA combination therapy was both more costly and more effective than LABA alone. The incremental cost effectiveness ratio for the ICS+LABA combination versus LABA in patients with at least moderate COPD was $261,539/QALY, in patients with at least severe COPD it was $98,911/QALY and in those with very severe COPD it was $79,448/QALY. With respect to the comparison of the ICS+LABA combination with ICS alone, the combination dominated ICS alone, being both less costly and more effective than ICS alone. The lack of cost effectiveness of ICS alone in COPD, however, does not support the use of this treatment strategy in COPD.

In comparison with LAMA alone, triple therapy is both more costly and more effective resulting in an incremental cost effectiveness ratio ranging from approximately $85,000/QALY to $160,000/QALY. As compared with LAMA+LABA given as dual therapy (two separate inhalers), triple therapy with an ICS+LABA combination with a LAMA resulted in a cost effectiveness ratio of $28,767 per QALY in patients with at least moderate COPD and triple therapy was the dominant therapy. Interpretation of these latter results should be put into context with the comparative cost effectiveness of the combination of LAMA+LABA versus LAMA alone. In most cases LAMA alone dominated the use of LAMA+LABA as it was both more effective and less costly.

The results within each of the subgroups (varied by age and gender) were consistent with those seen in the base case analysis. The results of the deterministic and probabilistic sensitivity analysis suggest the conclusions of the analysis are robust.

Reimbursement Based Economic Assessment

In 2012, there were a total of 205,825 COPD drug recipients with at least moderate COPD (30,600 with very severe disease, 28,707 with severe disease and 146,518 with moderate disease). Total expenditure

by OPDP on COPD therapy for patients with at least moderate COPD was $141.6 million. Expenditure on COPD therapy ranged from $23.6 million for patients with severe COPD to $87.6 million for patients with moderate COPD; patients with very severe COPD accounted for 4% of total costs or $30.4 million.

The largest component of this expenditure was for combination products including ICS and LABA which comprised of $80.6 million or 57% of drug expenditure. Total costs for combination products including ICS and LABA ranged from $14.3 million for patients with severe COPD to $48.0 million for patients with moderate COPD; for patients with very severe COPD, combination products including ICS and LABA accounted for 60% of drug expenditure or $18.3 million.

For each severity, ICS+LABA combination products were the most commonly prescribed drug product (75.2% of very severe patients, 69.5% of severe patients and 56.9% of moderate patients had at least one prescription for an ICS+LABA combination product). The most commonly prescribed ICS+LABA combination product was Advair Diskus with comprising 48.7% of all prescriptions for combination products.

A policy of listing ICS+LABA combination products licensed for COPD (Advair Diskus and Symbicort) as limited use for patients with very severe COPD will likely lead to a relatively small decline in total COPD therapy expenditures (a reduction of $8,427or 0.006%) based on a proportion of patients on dual ICS and LABA therapy moving to combination products. Expanding the limited use criteria to include at least severe or at least moderate COPD will have a slightly greater impact on total COPD therapy expenditure (a reduction of 0.012% and 0.034% respectively or a reduction of $17,540 and $48,277 respectively).

Conclusions

Due to concerns over the available studies, it is not possible to make any inferences based on the previously published studies on whether the use of ICS+LABA is cost effective for any COPD patients.

In patients receiving ICS and LABA via separate inhalers, this analysis suggests that moving to administration of the combination via a single inhaler is cost effective. However, the combination of ICS and LABA is not cost effective when compared with LABA alone. Triple therapy with ICS+LABA combination in addition to LAMA is not cost effective compared with LAMA alone.

Policies whereby ICS+LABA combination products were listed as a limited use benefit for COPD would lead to only modest savings with respect to the overall expenditure on COPD drug therapy. Cost savings would be greater if a discounted price for ICS+LABA combination products could be negotiated in combination with a more liberal listing.

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List of Abbreviations

CADTH	Canadian Agency for Drugs and Technologies in Health
CDN$	Canadian dollars
CEA	cost-effectiveness analysis
CIHI	Canadian Institute for Health Information
COP	Colombian Peso
COPD	chronic obstructive pulmonary disease
CUA	cost-utility analysis
DC	Doug Coyle
EAP	Exceptional Access Program
EQ-5D	European Quality of Life-5 Dimensions
FEV_1	Forced Expiratory Volume in 1 Second
ICER	incremental cost-effectiveness ratio
ICES	Institute for Clinical Evaluative Sciences
ICS	inhaled corticosteroids
ICUR	incremental cost-utility ratio
KAS	Kelley-Anne Sabarre
LABA	long-acting $beta_2$-agonist
ICS+LABA	inhaled corticosteroids in combination with long-acting $beta_2$-agonist
LAMA	long-acting anticholinergic
LY	life years
MOHLTC	Ontario Ministry of Health and Long-Term Care
N/A	not applicable
NCGC	National Clinical Guideline Centre
NHS	National Health Care System
NHSEED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
OPDP	Ontario Public Drug Plan
PDE-4	phosphodiesterase type 4 inhibitor
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
RCT	randomized controlled trial
RUSIC	Resource Utilization Study in COPD
SGRQ	St. George's Respiratory Questionnaire
USD$	American dollars

Acknowledgments

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Introduction

This report assesses the current evidence for the cost-effectiveness of ICS+LABA for chronic treatment of COPD and the economic impact of alternative changes to the funding status of ICS+LABA.

Research Questions

RQ1 What is the current evidence for the cost-effectiveness of ICS+LABA for chronic treatment of COPD compared to single or combination therapies incorporating LABA, LAMA and ICS?

RQ2 Based on a de novo economic model, what is the cost-effectiveness of ICS+LABA for chronic treatment of COPD compared to single and combination therapies incorporating LABA, LAMA and ICS?

RQ3 What is the economic impact of alternative policies for reimbursing ICS+LABA for chronic treatment of COPD?

Methods

Systematic Review of Published Economic Evaluations

To address RQ1, we conducted a systematic review of the available literature on the cost-effectiveness of ICS+LABA for the treatment of COPD compared to: single or combination therapies incorporating LABA, LAMA and ICS. The focus of the systematic critical review was on the strength and quality of evidence addressing the cost-effectiveness of ICS+LABA. The generalizability of the reports to OPDP is dependent on a number of methodological factors. Key issues in this review were whether the study adopted a Canadian perspective, modelled distinct COPD severity populations, modelled a lifetime time frame, and reported incremental cost-effectiveness ratios.

Search Strategy

A search of the medical literature from 1946 to present (2013 December 03) in Ovid Medline (indexed, in-process and other non-indexed) and Embase Classic & Embase 1947 to 2013 December 04 was conducted in order to capture all relevant literature. Key words relating to ICS+LABA for the treatment of COPD were combined with a standardized search strategy for identifying economic analyses adopted by National Health Service Economic Evaluation Database (NHS EED). The complete search strategy can be found in Appendix A1: Search Strategy.

In addition, citations included by manufacturers in their evidence submission packaged were screened; reasons for inclusion/exclusion can be found in Appendix A2: List of Citations Included by Manufacturer. As well, the Tufts CEA registry and NHSEED were searched for relevant articles. Grey literature was identified through the Canadian Agency for Drugs and Technologies in Health (CADTH) and National Institute for Health and Care Excellence (NICE) websites. Moreover, the reference lists of relevant studies were hand searched for additional relevant studies.

Search Findings

1183 citations were identified from the original search.

One reviewer (KAS) independently reviewed the literature searches in order to identify potential articles for inclusion within the critical appraisal. Any uncertainties were resolved through consensus with another reviewer (DC).

Of the 1183 citations that were identified from the original search, the two additional citations included by manufacturers, and the two identified from grey literature, a total of 104 economic citations were identified for potential inclusion within the report; 1034 citations were excluded. The reasons for exclusion were the following: not an economic analysis, not COPD, or not relevant intervention. An additional 49 citations were excluded; reasons for exclusion were as follows: non-English, not available or not full text. Results of the search can be found in Appendix A3: Results of Search.

The 104 potential studies identified during the literature review were reviewed by one reviewer (KAS). Of these, 9 publications which addressed the objective of the review were selected for inclusion. Those studies that were not included within the review along with the reasons for exclusion are detailed in Appendix A4: List of Excluded Studies.

De novo Economic Evaluation

To address RQ2, an independent de novo economic model was developed to assess the cost effectiveness of ICS, LABA and LAMA as single and combination therapies based on disease severity from the Canadian context.

The long term costs and quality adjusted life years (QALYs) of ICS plus LABA combination therapies compared to single or combination therapies incorporating LABA, LAMA and ICS in the treatment of COPD was assessed using a Markov model.

In modelling the disease progression in COPD, previous models have assessed disease severity by categorising patients by their FEV_1% which decreases with time, leading to transitions from milder to more severe states. Both rates of exacerbations and mortality have been shown to increase with disease severity and the proportion of exacerbations requiring hospitalizations similarly increases with severity. Thus, similar to previous models, the model is comprised of five mutually exclusive states representing COPD disease severity and death. Death is an absorbing state meaning that when individuals enter this state, they remain within the state. The four states of COPD severity are defined according to GOLD guideline criteria for COPD diagnosis which classifies disease severity based on post bronchodilator FEV_1.[1] Mild encompasses those patients with an FEV_1 greater than or equal to 80% of normal, moderate between 50% and 79% of normal, severe between 30% and 49% of normal and very severe between below 30% of normal.

The cycle length of the model is one month with a lifetime horizon (maximum of 30 years). The model is adaptable, allowing for the estimation of the costs and QALYs associated with COPD treatments in a cohort of patients at any age from 40 to 100 years and with any severity of COPD.

During each cycle of the model, patients in each of the disease model states may experience an exacerbation of their COPD, progression of their disease or die either due to COPD or due to other causes. Within the mild, moderate and severe states patients who experience an exacerbation may either progress to the next more severe state, die due to a hospital treated exacerbation, die due to background mortality or remain within the same COPD severity state. Patients who do not experience an exacerbation may progress to the next more severe state, die due to background mortality or remain within the same COPD severity state. Patients within the very severe state may experience the same outcomes, except they do not progress to a more severe COPD state.

Costs and QALYs are both discounted at a standard rate of 5% per annum.[5] The cost effectiveness of each of the treatments is then estimated as the cost per quality adjusted life year gained relative to the comparator treatment. A probabilistic sensitivity analysis (PSA) was conducted in order to estimate the impact of parameter uncertainty on the cost effectiveness. The results of the PSA are presented through 95% CI around outcomes and in a cost effectiveness acceptability curve depicting the probability each treatment option is the most cost effective given different threshold values for a QALY.

A detailed description of the economic model is provided in Appendix B – De novo Economic Evaluation.

Reimbursement Based Economic Assessment

Applied, Policy-Oriented Economic Model

To address RQ3, an applied, policy oriented economic model focusing on financial impact was created to facilitate consideration of alternative reimbursement strategies for COPD therapy. The analysis utilized OPDP data on usage of ICS, LABA, LAMA, and ICS+LABA from April 2011 to March 2012. COPD patients who were dispensed at least one prescription for a COPD therapy (LABA, LAMA, ICS, ICS+LABA) in Ontario were included in the analysis. The model was developed within Microsoft Excel.

First, COPD therapies were defined. Then, assumptions for the analysis were specified. Afterwards, alternative approaches to reimbursement of COPD therapy were identified. Strategies considered introducing limited use criteria for ICS+LABA combination products varying by COPD disease severity – Very Severe, At Least Severe, At Least Moderate.

A detailed description of the assumptions and model details can be found in Appendix C1– Model Details.

Then, budget expenditure on COPD treatments for each alternative reimbursement strategy was forecasted. Given the scope of the drug class review, aggregated COPD therapy expenditure and usage include ICS+LABA products in inhaled aerosol and inhaled powder form, while disaggregated ICS+LABA expenditure and usage data is restricted to inhaled powder.

Findings

Systematic Review of Published Economic Evaluations

Included Studies

Of the nine reports selected for inclusion, three were American,[4,6,7] three were European studies (UK, Italy), [3,8,9]one study was Canadian,[2] another from Colombia,[10] and one involved multiple regions (USA, Eastern Europe, Western Europe, and Asia/Pacific and other).[11] All but two were financed by pharmaceutical manufacturers,[2,6-11] five of which were sponsored by GlaxoSmithKline.[2,6,7,9-11] One study was sponsored by NICE,[3] while the other had no financial support.[4]

A total of two studies were cost-effectiveness analyses,[7,9] four were cost-utility analyses,[2-4,11] and the remaining three were both cost-effectiveness and cost-utility analyses.[6,8,10] More than half the studies considered monotherapy, dual therapy and placebo/no therapy,[4,6,7,9,11] two studies considered monotherapy versus dual therapy,[2,10] while one report considered monotherapy, dual therapy and triple therapy,[3] and another considered monotherapy, dual therapy and triple therapy along with combinations including a phosphodiesterase type 4 inhibitor (PDE-4) – roflumilast.[8] The most common monotherapy was LABA, followed by ICS and LAMA and only one study considered a dual therapy of LAMA+LABA. For this report, the focus is on results relating to single and combination therapies including LABA, LAMA and ICS.

Of the nine relevant reports, seven were Markov models,[2-4,6,8-10] one was a trial based analysis, [11] and one was based on an analysis of an observational cohort.[7] Of Markov model based analyses, one had a cycle length of one month,[8] while three used a cycle length of three months,[2,4,10] and the remaining three used a one year cycle length.[3,6,9] Eight studies considered a health care system or third party payer perspective,[2-4,6-8,10,11] and one a societal perspective.[9]

Within the models, COPD severity was assessed based on a variety of classifications: including the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria,[3,4,8-10] the American Thoracic Society criteria,[2,6] a specified Forced Expiratory Volume in 1 Second (FEV_1) predicted value,[11] and a non-specified FEV_1 predicted value. [7] Only two studies considered populations with a distinct degree of COPD severity.[2,8] Four studies specified an age range (20 years old and over,[9] 40 years old and over,[7] aged 40-80[6,11]), while four specified a mean or starting age (range of between 61-66 years of age)[2-4,8] and one did not specify the age of the population modelled.[10]

Of the nine relevant reports, five studies considered a lifetime horizon [2,6-9] and the remaining four considered a time horizon of five years or less.[3,4,10,11] Two studies used effectiveness data from published network meta-analysis or mixed treatment comparison,[8,10] one study used a published observational cohort study,[7] and the rest used single or multiple randomized controlled trials.[2-4,6,9,11]

Before summarizing the modelling of the natural history of COPD within the economic models, there are a number of issues that must be highlighted. Disease severity is often assessed by categorising patients

by their FEV_1% which decreases with time leading to transitions from milder to more severe states. Rates of exacerbations have been shown to increase with disease severity and the proportion of exacerbations requiring hospitalizations similarly increases with severity. Mortality has been shown to be related to hospitalization for exacerbations (which also increases with age) and has been shown to increase with disease severity – this latter increase occurs not just due to the increased rate of hospitalizations due to exacerbations though the forecasted increase in mortality due to disease severity must be parsed into that occurring as a result of exacerbations and that occurring independently from exacerbations. Thus, in modelling the natural history of COPD, inclusion of both mortality due to hospitalizations from exacerbations and unadjusted increases in mortality from disease severity are liable to double counting of the mortality effect from disease progression. The nature of the progression of COPD makes the modelling of treatment effects similarly prone to double counting. Incorporating the effect of treatment on FEV_1%, will lead to delay in transitions across disease severity and thus an indirect effect on both exacerbation rates and mortality. Incorporating the effect of treatment on exacerbations will have an indirect effect on mortality due to reduced hospitalized exacerbations; assuming mortality due to exacerbations is incorporated. Thus, analyses which incorporate any two of the effect of treatment on FEV_1%, exacerbations and mortality will involve double counting of treatment effects and bias in the estimates of cost effectiveness.

Of the seven Markov model based analyses, four studies modelled the effect of treatment on the rates of exacerbation,[2,3,8,9] two studies incorporated the treatment effect on both mortality and exacerbations though assumed no increase in mortality with exacerbations,[4,6] while the last study modelled treatment effect using both FEV_1 and exacerbation, thus, double counting the benefits of treatment.[10] None of the reports included adverse events in the model.

Eight studies assessed cost effectiveness in terms of life years and/or quality-adjusted life years (QALYs) gained used final endpoints,[2-4,7,8,10,11] while one used only an intermediate outcome (exacerbations avoided).[9] Of the reports which considered final endpoints, one study involved double counting of mortality by incorporating both increased mortality with disease severity using standardized morality rates and mortality due to hospital-treated exacerbations. [8]

Of the seven reports which considered utility values, four were derived from the EQ-5D,[2,8,10,11] one used St. George's Respiratory Questionnaire (SGRQ) scores to map to the EQ-5D,[4] and two used both the EQ-5D and the mapping of SGRQ scores to the EQ-5D.[3,6] Six of the seven modelling studies conducted both deterministic and probabilistic sensitivity analyses,[2-4,6,8,10] while one only conducted deterministic analysis.[9] The one randomized controlled trial (RCT) based study and one observational data study used the bootstrap method to assess uncertainty.[7,11]

All of the reports used branded prices and did not consider future generic prices in the analysis.

In terms of results, five studies reported meaningful results in terms of incremental cost effectiveness in terms of QALYs or life years gained for relevant treatment options.[2,3,7,10,11] One studies reported results in terms of intermediate outcomes,[9] two studies only reported incremental cost effectiveness ratios for

no treatment compared to alternative treatments,[4,6] and one only reported results in the form of estimated costs and outcomes which precluded the ability to estimate incremental cost effectiveness ratios.[8]

A table summarizing included studies is provided in Appendix A6: Characteristics of Reviewed Studies. Thus, given the above, the quality of each study was assessed in terms of: the source of effectiveness data; whether cost effectiveness was measured in terms of final outcomes; the appropriateness of modelling disease progression and mortality; the appropriateness of modelling treatment effect; and the adoption of sensitivity analysis.

The applicability of each study was assessed in terms of: sponsorship, time horizon, perspective, COPD severity population modelled, and reporting of results.

Overall Conclusions

Overall, the studies identified in this review are of limited applicability to the current Canadian setting. Only two studies used effectiveness data from published network meta-analysis or mixed treatment comparison, one study used a published observational cohort study, and many used a single or selection of randomized controlled trials. For some CUAs, non-utility measures were used to indirectly calculate QALYs. All but two studies were industry sponsored.

Only one Canadian study was found.[2] Its results suggest that ICS+LABA was more cost effective than LABA alone in patients with Stage 3 COPD (based on the American Thoracic Society criteria), though its cost effectiveness in patients with Stage 1 and Stage 2 was unclear. The applicability of this study relates primarily to the potential for bias in assumptions and input relating to study sponsorship.

Of the non-Canadian studies, three were cost-effectiveness analyses, three were cost-utility analyses, and three were cost-effectiveness/utility analyses.

The studies conducted by NCGC[3] and Oba[4] were independent of manufacturer sponsorship. Both studies compare ICS+LABA to a variety of comparators. The population modelled in the analysis by NCGC was patients with severe to very severe COPD (based on the GOLD criteria) with a mean age of 66, while patients with moderate to very severe COPD (based on the GOLD criteria) with a mean age of 65 were modelled in the analysis by Oba. In both studies, the model had a limited time horizon (three and four year time frames).

The results of the NCGC report varied depending on the source of effectiveness data which limits its usefulness in decision making. The study by Oba which evaluated the cost effectiveness of ICS+LABA compared to monotherapies (LABA or ICS) and placebo only used effectiveness data derived from a single randomized controlled trial and the lack of transparency in reporting questions its applicability. Results from all manufacturer sponsored economic analyses favoured the manufacturer's treatment.

Overall, most studies compared ICS+LABA to placebo, LABA, and ICS, fewer studies examined the cost effectiveness of ICS+LABA versus LAMA, LAMA+LABA, and triple therapy (ICS+LABA +LAMA). Applicability of non-Canadian studies to any decision regarding the cost effectiveness of ICS+LABA is limited given they are not from the Canadian perspective; all except for two are industry sponsored and favour the manufacturer's therapy.

A full systematic review report can be found in Appendix A - A Systematic Review of Published Economic Evidence.

Given both contradictory results and the consistent concerns over the quality and the relevance of the available studies, it is not possible to make any inferences on which patient population the use of ICS+LABA is cost effective.

As a result, to assist with the ODPRN review, an independent de novo economic model was conducted to address the cost effectiveness of alternative reimbursement strategies for ICS in combination with LABA compared the current strategy.

De novo Economic Evaluation

Base Case

With respect to the comparative cost effectiveness of ICS+LABA combination versus ICS and LABA as dual therapy the lack of clinical data precluded the inclusion of this comparison within the network meta-analysis. Therefore, based on the lack of evidence within the systematic review, it was assumed that there is no difference in efficacy or adverse events between administration of an ICS and LABA via a single inhaler and administration via two separate inhalers, and a cost minimization analysis was conducted. In the case of both the budesonide/formoterol combination and the fluticasone/salmeterol combination, the cost of the single inhaler combination product is lower than the cost of receiving the two medications via separate inhalers.

In all severities of COPD, ICS+LABA combination therapy was both more costly and more effective than LABA alone. The incremental cost effectiveness ratio for the ICS+LABA combination versus LABA in patients with at least moderate COPD was $261,539/QALY, in patients with at least severe COPD it was $98,911/QALY and in those with very severe COPD it was $79,448/QALY. Based on a willingness to pay threshold of $50,000/QALY the ICS+LABA combination would not be considered cost effective as compared with LABA alone in any of these patient populations. With respect to the comparison of the ICS+LABA combination with ICS alone, the combination dominated ICS alone, being both less costly and more effective than ICS alone. The lack of cost effectiveness of ICS alone in COPD, however, does not support the use of this treatment strategy in COPD.

In comparison with LAMA alone, triple therapy is both more costly and more effective resulting in an incremental cost effectiveness ratio ranging from approximately $85,000/QALY to $160,000/QALY. At a willingness to pay threshold of $50,000/QALY, triple therapy with ICS+LABA combination with LAMA would not be considered cost effective compared with LAMA alone.

As compared with LAMA+LABA given as dual therapy (two separate inhalers), triple therapy with an ICS+LABA combination with a LAMA resulted in a cost effectiveness ratio of $28,767 per QALY in

patients with at least moderate COPD and triple therapy was the dominant therapy, meaning it was both more effective and less costly, in patients with at least severe or very severe COPD. Interpretation of these results should be put into context given the lack of cost effectiveness of the combination of LAMA+LABA versus LAMA alone.

Overall Conclusions

In patients receiving ICS and LABA via separate inhalers, this analysis supports the cost effectiveness of moving to administration of the combination via a single inhaler.

This analysis did not, however, find the combination product of ICS and LABA to be cost effective when compared with LABA alone. Additionally, the analysis did not find triple therapy with ICS+LABA combination in additional to LAMA cost effective when compared with LAMA alone.

Reimbursement Based Economic Assessment

Current Usage and Expenditure

In 2012, total expenditure by OPDP on COPD therapy (defined as long-acting bronchodilator therapy i.e., LAMA, LABA, ICS and ICS+LABA) for patients with at least moderate COPD was $141.6 million. Expenditure on COPD therapy ranged from $23.6 million for patients with severe COPD to $87.6 million for patients with moderate COPD; patients with very severe COPD accounted for 4% of total costs or $30.4 million.

The largest component of this expenditure was for combination products including ICS and LABA which comprised of $80.6 million or 57% of drug expenditure. Total costs for combination products including ICS and LABA ranged from $14.3 million for patients with severe COPD to $48.0 million for patients with moderate COPD; for patients with very severe COPD, combination products including ICS and LABA accounted for 60% of drug expenditure or $18.3 million. It should be noted that in Ontario, three ICS+LABA products (i.e., fluticasone+salmeterol, budesonide+formoterol, mometasone+formoterol) are available on the Ontario Drug Benefit formulary only for the treatment of asthma under the Limited Use program; there is no LU code for COPD.

The most commonly prescribed COPD therapy was ICS+LABA combination products. In 2012, there were a total of 205,825 COPD drug recipients with at least moderate COPD (30,600 with very severe disease, 28,707 with severe disease and 146,518 with moderate disease). For each severity, ICS+LABA combination products was the most commonly prescribed drug product (75.2% of very severe patients, 69.5% of severe patients and 56.9% of moderate patients had at least one prescription for an ICS+LABA combination product). The most commonly prescribed ICS+LABA combination product was Advair Diskus with comprising 48.7% of all prescriptions for combination products.

The average cost per unit was for COPD therapy ranged from $0.57 for ICS to $2.26 for LAMA. The average cost per unit for ICS+LABA varied from $0.55 for Symbicort 100MCG to $2.46 for Advair Diskus 500MCG.

Alternative Approaches to Reimbursement Considered

The following is a summary of the reimbursement strategies, for full details of all reimbursement strategies refer to Appendix B Table 7 Reimbursement Strategies.

LU1-LU3 – Combination ICS+LABA therapy moved to limited use (LU) for COPD, costs were estimated by assuming 20% of current users on triple therapy (dual) or dual therapy (ICS + LABA) would move to combination therapy (ICS+LABA) assuming variable coverage by COPD severity [very severe, at least severe, at least moderate].

LU4-LU6 – A single combination ICS+LABA therapy moved to limited use (LU) for COPD (Advair Diskus(**A**) or Symbicort(**S**)), costs were forecasted by assuming 20% of current triple or dual therapy users would move to the single combo covered assuming variable coverage by COPD severity [very severe, at least severe, at least moderate].

LU7-LU9 - A single combination ICS+LABA therapy moved to limited use (LU) for COPD (Advair Diskus(A) or Symbicort(S)), other single combination to EAP. Assume 20% of current dual or triple therapy users on Alvesco and move to LU covered combo, while 20% of current dual or triple therapy users of Flovent and Pulmicort move to combo version assuming variable coverage by COPD severity [very severe, at least severe, at least moderate].

Impact of Alternative Approaches to Reimbursement

In 2012, the total expenditure on COPD therapy (ICS, LABA, ICS+LABA, LAMA) was $141.6 million.

A policy of listing ICS+LABA combination products licensed for COPD (Advair Diskus and Symbicort) as limited use for patients with very severe COPD will likely lead to a relatively small decline in total COPD therapy expenditures (a reduction of $8,427or 0.006%) based on a proportion of patients on dual ICS and LABA therapy moving to combination products. Expanding the limited use criteria to include at least severe or at least moderate COPD will have a slightly greater impact on total COPD therapy expenditure (a reduction of 0.012% and 0.034% respectively or a reduction of $17,540 and $48,277 respectively).

An alternate policy whereby only Advair Diskus was listed as a limited use product combined with a 20% price reduction was considered. This was forecasted to lead to a greater decline in total costs ranging from 1.472%-6.064% (savings of $2.1 million for users with very severe COPD, $3.6 million for users with at least severe COPD, $8.6 million for users with at least moderate COPD). A similar policy but in addition listing Symbicort under EAP would lead to similar results.

A similar policy but with Symbicort listed as a limited use product combined with a 20% price reduction would lead to a reduction in total costs ranging from 0.480%-2.658% (savings of $0.7 million for users with very severe COPD, $1.4 million for users with at least severe COPD, $3.8 million for users with at least moderate COPD). Allowing in addition Advair Diskus to be covered under EAP, would lead to a similar reduction in costs.

The analysis is most sensitive to price reduction. With a 20% price reduction, having a preferred product would lead to a reduction in COPD therapy costs of between 2.655% and 6.077% if applied to all with at least moderate COPD. However, if there was no reduction in the cost of the preferred product, the cost reduction would be between 0.004% and 0.079%. With a preferred product, if all users of triple therapy dual and dual therapy (ICS + LABA) moved to combination therapy, the cost reduction would be between 1.137% and 6.312%. Similarly, if all users of triple therapy dual and dual therapy (ICS + LABA) moved to combination therapy and no reduction in the cost of the preferred product, the cost reduction would be between 0.02% and 0.397%.

A full budget impact analysis report can be found in Appendix C – Budget Impact Analysis.

Overall Conclusions

In 2012, the total expenditure on COPD therapy (ICS, LABA, ICS+LABA, LAMA) was $141.6 million.

Covering a single ICS+LABA combination therapy under LU with a negotiated price reduction for those with at least moderate COPD would lead to a small absolute decrease in total COPD therapy expenditure. Covering both ICS+LABA combination therapies under LU will lead to a smaller decrease in expenditure.

Conclusions

Moving combination products to LU, whereby users of dual therapy (ICS + LABA) or triple therapy (dual) with at least moderate COPD may move to combination products will lead to minimal cost savings given the high current use of combination products within these degrees of COPD severity.

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Appendices
Appendix A - A Systematic Review of Published Economic Evidence

Research Question

What is the current evidence for the cost-effectiveness of ICS in combination with LABA (ICS+LABA) for chronic treatment of chronic obstructive pulmonary disease (COPD) compared to single or combination therapies incorporating long-acting beta$_2$-agonist (LABA), long-acting anticholinergic (LAMA) and inhaled corticosteroids (ICS)?

Review of the Published Literature

Search Strategy and Search Findings

Search Strategy

A search of the medical literature from 1946 to present (2013 December 03) in Ovid Medline (indexed, in-process and other non-indexed) and Embase Classic & Embase 1947 to 2013 December 04 was conducted in order to capture all relevant literature. Key words relating to ICS+LABA for the treatment of COPD were combined with a standardized search strategy for identifying economic analyses adopted by National Health Service Economic Evaluation Database (NHS EED). The complete search strategy can be found in Appendix A1: Search Strategy.

In addition, citations included by manufacturers in their evidence submission packaged were screened; reasons for inclusion/exclusion can be found in Appendix A2: List of Citations Included by Manufacturer. As well, the Tufts CEA registry and NHSEED were searched for relevant articles. Grey literature was identified through the Canadian Agency for Drugs and Technologies in Health (CADTH) and National Institute for Health and Care Excellence (NICE) websites. Moreover, the reference lists of relevant studies were hand searched for additional relevant studies.

Search Findings

1183 citations were identified from the original search.

One reviewer (KAS) independently reviewed the literature searches in order to identify potential articles for inclusion within the critical appraisal. Any uncertainties were resolved through consensus with another reviewer (DC).

Of the 1183 citations that were identified from the original search, the two additional citations included by manufacturers, and the two identified from grey literature, a total of 104 economic citations were identified for potential inclusion within the report; 1034 citations were excluded. The reasons for exclusion were the following: not an economic analysis, not COPD, or not relevant intervention. An additional 49 citations were excluded; reasons for exclusion were as follows: non-English, not available or not full text. Results of the search can be found in Appendix A3: Results of Search.

The 104 potential studies identified during the literature review were reviewed by one reviewer (KAS). Of these, 9 publications which addressed the objective of the review were selected for inclusion. Those

studies that were not included within the review along with the reasons for exclusion are detailed in Appendix A4: List of Excluded Studies.

Included Studies

The comprehensive list of included studies can be found in Appendix A5: List of Included Studies.

Summary and Critical Appraisal of Included Studies: COPD

Included Studies

Of the nine reports selected for inclusion, three were American,[4,6,7] three were European studies (UK, Italy), [3,8,9]one study was Canadian,[2] another from Colombia,[10] and one involved multiple regions (USA, Eastern Europe, Western Europe, and Asia/Pacific and other).[11] All but two were financed by manufacturers,[2,6-11] five of which were sponsored by GlaxoSmithKline.[2,6,7,9-11] One study was sponsored by NICE,[3] while the other had no financial support.[4]

A total of two studies were cost-effectiveness analyses,[7,9] four were cost-utility analyses,[2-4,11] and the remaining three were both cost-effectiveness and cost-utility analyses.[6,8,10] More than half the studies considered monotherapy, dual therapy and placebo/no therapy,[4,6,7,9,11] two studies considered monotherapy versus dual therapy,[2,10] while one report considered monotherapy, dual therapy and triple therapy,[3] and another considered monotherapy, dual therapy and triple therapy along with combinations including a phosphodiesterase type 4 inhibitor (PDE-4) – roflumilast.[8] The most common monotherapy was LABA, followed by ICS and LAMA and only one study considered a dual therapy of LAMA+LABA. For this report, the focus is on results relating to single and combination therapies including LABA, LAMA and ICS.

Of the nine relevant reports, seven were Markov models[2-4,6,8-10], one was a trial based analysis [11] and one was based on an analysis of an observational cohort.[7] Of Markov model based analyses, one had a cycle length of one month,[8] while three used a cycle length of three months,[2,4,10] and the remaining three used a one year cycle length.[3,6,9] Eight studies considered a health care system or third party payer perspective,[2-4,6-8,10,11] and one a societal perspective.[9]

Within the models, COPD severity was assessed based on a variety of classifications: including the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria,[3,4,8-10] the American Thoracic Society criteria,[2,6] a specified Forced Expiratory Volume in 1 Second (FEV_1) predicted value,[11] and a non-specified FEV_1 predicted value. [7] Only two studies considered populations with a distinct degree of COPD severity.[2,8] Four studies specified an age range (20 years old and over,[9] 40 years old and over,[7] aged 40-80[6,11]), while four specified a mean or starting age (range of between 61-66 years of age)[2-4,8] and one did not specify the age of the population modelled.[10]

Of the nine relevant reports, five studies considered a lifetime horizon [2,6-9] and the remaining four considered a time horizon of five years or less.[3,4,10,11] Two studies used effectiveness data from published network meta-analysis or mixed treatment comparison,[8,10] one study used a published observational cohort study,[7] and the rest used single or multiple randomized controlled trials.[2-4,6,9,11]

Before summarizing the modelling of the natural history of COPD within the economic models, there are a number of issues that must be highlighted. Disease severity is often assessed by categorising patients by their FEV_1% which decreases with time leading to transitions from milder to more severe states. Rates of exacerbations have been shown to increase with disease severity and the proportion of exacerbations requiring hospitalizations similarly increases with severity. Mortality has been shown to be related to hospitalization for exacerbations (which also increases with age) and has been shown to increase with disease severity – this latter increase occurs not just due to the increased rate of hospitalizations due to exacerbations though the forecasted increase in mortality due to disease severity must be parsed into that occurring as a result of exacerbations and that occurring independently from exacerbations. Thus, in modelling the natural history of COPD, inclusion of both mortality due to hospitalizations from exacerbations and unadjusted increases in mortality from disease severity are liable to double counting of the mortality effect from disease progression. The nature of the progression of COPD makes the modelling of treatment effects similarly prone to double counting. Incorporating the effect of treatment on FEV_1%, will lead to delay in transitions across disease severity and thus an indirect effect on both exacerbation rates and mortality. Incorporating the effect of treatment on exacerbations will have an indirect effect on mortality due to reduced hospitalized exacerbations; assuming mortality due to exacerbations is incorporated. Thus, analyses which incorporate any two of the effect of treatment on FEV_1%, exacerbations and mortality will involve double counting of treatment effects and bias in the estimates of cost effectiveness.

Of the seven Markov model based analyses, four studies modelled the effect of treatment on the rates of exacerbation,[2,3,8,9] two studies incorporated the treatment effect on both mortality and exacerbations though assumed no increase in mortality with exacerbations,[4,6] while the last study modelled treatment effect using both FEV_1 and exacerbation, thus, double counting the benefits of treatment.[10] None of the reports included adverse events in the model.

Eight studies assessed cost effectiveness in terms of life years and/or quality-adjusted life years (QALYs) gained used final endpoints,[2-4,7,8,10,11] while one used only an intermediate outcome (exacerbations avoided).[9] Of the reports which considered final endpoints, one study involved double counting of mortality by incorporating both increased mortality with disease severity using standardized morality rates and mortality due to hospital-treated exacerbations. [8]

Of the seven reports which considered utility values, four were derived from the EQ-5D,[2,8,10,11] one used St. George's Respiratory Questionnaire (SGRQ) scores to map to the EQ-5D,[4] and two used both the EQ-5D and the mapping of SGRQ scores to the EQ-5D.[3,6] Six of the seven modelling studies conducted both deterministic and probabilistic sensitivity analyses,[2-4,6,8,10] while one only conducted deterministic analysis.[9] The one randomized controlled trial (RCT) based study and one observational data study used the bootstrap method to assess uncertainty.[7,11]

All of the reports used branded prices and did not consider future generic prices in the analysis.

In terms of results, five studies reported meaningful results in terms of incremental cost effectiveness in terms of QALYs or life years gained for relevant treatment options.[2,3,7,10,11] One studies reported results in terms of intermediate outcomes[9], two studies only reported incremental cost effectiveness ratio for no treatment compared to alternative treatments[4,6], and one only reported results in the form of estimated costs and outcomes which precluded the ability to estimate incremental cost effectiveness ratios.[8]

A table summarizing included studies is provided in Appendix A6: Characteristics of Reviewed Studies. Thus, given the above, the quality of each study was assessed in terms of: the source of effectiveness data; whether cost effectiveness was measured in terms of final outcomes; the appropriateness of modelling disease progression and mortality; the appropriateness of modelling treatment effect; and the adoption of sensitivity analysis.

The applicability of each study was assessed in terms of: sponsorship, time horizon, perspective, COPD severity population modelled, and reporting of results.

Common Issues and Considerations

Only two studies considered distinct COPD severity populations in their model. In one of these studies, only patients with severe COPD (based on the GOLD criteria) were modelled. In the other report, three different analyses were conducted using different populations: patients with Stage 3, patients with Stage 2 and 3, and patients with all Stages of COPD based on the American Thoracic Society criteria. Analysis by disease severity is of vital importance to reimbursement decisions as cost effectiveness and hence, reimbursement can vary by severity.

There is a lack of independent studies conducted on the cost effectiveness of ICS+LABA compared to single or combination therapies incorporating LABA, LAMA and ICS. All but two studies identified were industry sponsored studies and these may be susceptible to the biases and limitations that have been found in manufacturer sponsored evaluations.[12]

All nine studies used branded prices for ICS+LABA, as manufacturer sponsored studies tend to be conducted at the point of seeking formulary reimbursement. Currently in Canada, ICS+LABA combinations are not available in generic form. However, the patent for Advair Diskus is expected to expire in June 30, 2014; while patents for Symbicort and Advair are expected to expire in 2019 and 2020. Therefore, the results of studies which include Advair Diskus may have limited applicability to future ICS+LABA expenditure unless reanalysis using approximates of generic prices is feasible.

All except for one study clearly considered ICS+LABA combination products. It is unclear with one study,[7] whether a fixed dose combination product was considered since data were derived from a published observational cohort study that did not specify whether ICS+LABA combination or ICS + LABA was the treatment.[13] Thus, the cost effectiveness of ICS+LABA as a combination therapy versus dual therapy cannot be assessed from the literature.

Many studies used effectiveness data derived from a single randomized controlled trial and one study used a published observational cohort study. Two studies did use effectiveness data from published network meta-analysis or mixed treatment comparison. Analysis which incorporates all the available evidence of treatment efficacy is needed.

Additionally, at times, treatment effect and morality were not modelled appropriately. Treatment effect on FEV_1, exacerbation and on mortality can be used to model drug-specific effect. However, as explained above, if more than one of these outcomes are considered, treatment effect may be overestimated. Similarly, the nature of disease progression within COPD means that morality rates may be modelled inappropriately if both standardized morality rates and morality due to hospital-treated exacerbations are modelled and not adjusted accordingly.

In certain studies, intermediate outcomes rather than final endpoints were used in the model. As COPD is a chronic disease, the use of intermediate outcomes (exacerbation avoided) does not yield meaningful results since long term effects are not considered.

Lastly, some studies used SGRQ to map the EQ-5D to calculate QALYs. SGRQ is a disease specific measure and therefore the appropriateness of any mapping from the SGRQ to utility values needs to be considered.

Canadian Studies

Chuck et al. (2008)

A study in 2008 by Chuck and colleagues sponsored by GlaxoSmithKline was a cost-utility analysis of LABA (formoterol 12 µg, salmeterol 50 µg) in comparison to ICS+LABA (salmeterol 50 µg/fluticasone propionate 250 µg, salmeterol 50 µg/fluticasone propionate 500 µg, budesonide 200 µg/formoterol 6 µg) in COPD patients with Stage 1 (FEV_1% ≥ 50% of predicted), Stage 2 (FEV_1% 35%-49.9% predicted) or Stage 3 (FEV_1% > 35%) disease based on the American Thoracic Society criteria. The reduction in FEV_1 over time was derived from The Lung Health Study Research Group.[14] This leads to transitions between severity states over time relating to disease progression. The analysis was from a Canadian health systems perspective.[2] The study was conducted using a Markov model with a three year and a lifetime time frame and a three month cycle length. Treatments were assumed to impact rates of exacerbations. Mortality and the rate of exacerbation increased with disease severity and utility loss occurred due to exacerbations and increased with disease progression. Three different groups of patients were entered into the model: COPD patients with Stage 3, COPD patients with Stage 2 and 3, and all Stage of COPD. The efficacy of the treatments were based on a meta-analysis of four published clinical trials.[15-18] Utility values for exacerbations were derived from the EQ-5D. Costs included within the model were routine maintenance costs, costs resulting from exacerbations and treatment regimens which were based on published Canadian sources.

Strengths of this analysis include that it is from a Canadian perspective incorporating Canadian costs and utility values derived from preference-based measures. As well, final outcomes (QALYs) were considered and analysis by disease severity was included. The model was well designed and reflective of the course

of disease with well referenced parameter inputs. Limitations of this analysis include that discounting rates were not reflective of Canadian guidelines.[5] Probabilistic analysis results were not particularly useful, as inappropriate distributions were used to handle uncertainty regarding parameter inputs.[19] The model did not incorporate any increased mortality associated with hospitalized exacerbations.

All results were presented in 2006 Canadian dollars. Using a three year time frame, the incremental cost effectiveness ratios for ICS+LABA (Stage 3, Stage 2 and 3, and all Stages) versus LABA were $39,000/QALY, $47,500/QALY, and $450,333/QALY. Using a lifetime horizon, the incremental cost effectiveness ratios for ICS+LABA (Stage 3, Stage 2 and 3, and all Stages) versus LABA were $25,333/QALY, $50,571/QALY, and $448,571/QALY. In sensitivity analyses, results for both time horizons were insensitive to incorporating the relative risk in all-cause mortality and to the exclusion of one study.[15] At a threshold of $50,000/QALY, the probability of ICS+LABA (for Stage 3, for Stage 2 and 3, and for all Stages) being more cost effective than LABA was 80%, 55%, and was never more cost effective than LABA alone, respectively.

This study reported meaningful results in the form of cost effectiveness ratios from ICS+LABA versus LABA, considered distinct COPD severity population, and is from a Canadian perspective. However, this study is industry sponsored and therefore may be susceptible to the biases and limitations that have been found in manufacturer sponsored evaluations.[12] Furthermore, the study was conducted in 2006 and incorporated only four clinical trials and did not include LAMA as a treatment option. As a result, the applicability of this study to any decision regarding the cost effectiveness of ICS+LABA should be made with caution.

Non-Canadian Studies

Guillermo Ariza et al. (2012)

Guillermo Ariza and associates compared the cost effectiveness of ICS+LABA (salmeterol/fluticasone), ICS+LABA (formoterol/budesonide), LABA (indacaterol), and LAMA (tiotropium) from a Colombian health care payer perspective.[10] Using the GOLD criteria, patients with mild to very severe COPD were modelled.

It was assumed, using data from the OLIN study that annual lung function declined;[20] and normal lung function was compared to the predicted lung function for patients with COPD to estimate FEV_1%. All-cause mortality by disease severity was modelled and treatment effect was modelled using both FEV_1 and exacerbation. Effectiveness data were derived from a published network meta-analysis for LABA versus ICS+LABA[21] and a published randomized controlled trial from LABA versus LAMA.[22] However, the effect of ICS+LABA on exacerbation rates was assumed to be the same as LABA rather than derived from the literature. Costs included within the model were drug acquisition costs, costs of maintenance therapy (other medication, physician visits, radiologic and laboratory tests) and cost of exacerbation (dependent on severity, may include ambulatory and emergency visits) which were based on published literature and expert opinion.

LABA was less costly and more effective and therefore, dominated ICS+LABA. Limited sensitivity analyses were conducted. Results from probabilistic analysis suggest that 65.7% of 1000 simulations indicated that LABA was less costly and more effective than salmeterol/fluticasone and 94.5% for LABA compared to formoterol/budesonide.

Strengths of this analysis include that it considered final outcomes (QALYs) and for LABA versus ICS+LABA, effectiveness in terms of improvement in FEV_1 data were derived from a published network meta-analysis. However, a major limitation of this analysis is that treatment effect was overestimated since both FEV_1 and exacerbation were used to model treatment effect.

Although this study considered the cost-effectiveness of ICS+LABA compared to LABA, applicability of this study is limited given that it is not an independent study, it is of a limited time horizon (five years), it is not from the Canadian perspective, and distinct COPD severity populations were not considered.

Hertel et al. (2012)

Hertel and colleagues compared the cost effectiveness of monotherapies (LAMA, LABA), dual therapies (ICS+LABA, LAMA+LABA) and triple therapy (LAMA+ ICS+LABA); as well as combinations including roflumilast from a UK health care system (NHS) perspective.[8] Results relating to roflumilast are not considered given the scope of this review. Using the GOLD criteria, patients with severe COPD were entered into the model. Transition probabilities for progression were based on the rate of FEV_1 decline relative to the natural decline in lung function in general population, while mortality was modelled using standardized mortality ratio for COPD and mortality due to hospital-treated exacerbations. Effectiveness was measured in terms of reduction in exacerbations only and effectiveness data were derived from a published mixed treatment comparison.[23] Costs included within the model were costs of drugs, costs cost of maintenance, and costs of community- and hospital treated exacerbations.

The study included two separate analyses: ICS tolerant patients and ICS intolerant patients – only the results for ICS tolerant were considered given the scope of this review. The treatments pertinent to this review ranked in terms of their estimated QALYs (from lowest to highest) were LABA, LAMA, ICS+LABA, LAMA+LABA and ICS+LABA + LAMA. The treatments had the same ranking in terms of estimated lifetime costs. However, incremental cost effectiveness ratios for the relevant comparisons were not provided and the data provided was insufficient to accurately infer these ratios.

Strengths of this study include the use of effectiveness data derived from a published mixed treatment comparison, the consideration of final outcomes (QALYs and life years, the variety of comparators considered (monotherapy, dual therapy, and triple therapy), preference-based utility measures were considered, and the extensive sensitivity analysis. The study had key limitations: mortality was not modelled appropriately and the probabilistic sensitivity analysis was not sufficiently described which limits its interpretability.

Although this report modelled a distinct COPD severity population, its applicability is limited given it is not an independent study, it is not from the Canadian perspective, and results are not reported in a manner which allows estimation of cost effectiveness.

Briggs et al. (2010)

Briggs and associates compared the cost effectiveness of ICS+LABA (fluticasone propionate 500 µg/salmeterol 50 µg), LABA (salmeterol 50 µg), ICS (fluticasone propionate 500 µg), and placebo from a health care system perspective.[11] The analysis was based on a multinational clinical trial and included five separate analyses: USA, Eastern Europe, Western Europe, Asia/Pacific and other, and a pool analysis. COPD patients with less than 60% FEV_1 predicted were populated in the trial based model. Effectiveness data were derived from a published randomized controlled trial.[15] Efficacy measures were all-cause mortality and quality of life. Costs included within the model were study medication and other costs (COPD hospitalization, non-COPD hospitalization, physician visits for COPD, telephone contacts for COPD, long-term oxygen therapy and concomitant medication); these costs were estimated using generalized linear models.[24]

Using regional costs, the incremental cost utility ratio for ICS+LABA versus placebo ranged from $21,500/QALY for Asia/Pacific and Other to $ 77,100/QALY for USA and for ICS+LABA versus LABA ranged from $13,000/QALY for Western Europe to $46,300/QALY for USA. Results from the non-parametric bootstrap suggest that at a willingness to pay of $50,000/QALY, ICS+LABA has the greatest probability of being the most cost effective treatment (93%) in the Western European region.

This analysis considered final outcomes (QALYs) and preference-based utility measures and estimates of cost and QALYs were obtained using appropriate statistical techniques. However, effectiveness data were derived from a single study and the nature of trial based studies makes it difficult to replicate the study results and to generalize the results to other geographical settings.

Although this study considers the cost-effectiveness of ICS+LABA compared to LABA and placebo/no therapy, applicability of this study is limited given that it is not an independent study, it is of a limited time horizon (three years), it is not from the Canadian perspective, and distinct COPD severity populations were not considered.

National Clinical Guideline Centre, (2010)

A study in 2010 by the National Clinical Guideline Centre (NCGC) was a cost-utility analysis of LAMA (tiotropium), ICS+LABA (budesonide/formoterol, fluticasone/salmeterol) and LAMA+ICS+LABA (tiotropium + budesonide/formoterol, tiotropium + fluticasone/salmeterol) in patients with severe to very severe COPD based on the GOLD criteria.[3] The analysis was from a UK NHS perspective. The study was conducted using a Markov model with a four year time frame and a one year cycle length. Patients entered the model at age 66. In the base case analysis, it was assumed that treatments had a differential effect on exacerbations only; however, differential treatment effects on mortality and quality of life were considered in the sensitivity analysis. Mortality was modelled using mortality risk by GOLD stage compared to the general population. The effectiveness of the treatments was based on three clinical

trials using direct and indirect comparisons; three separate analyses were conducted using combinations of the three trials. For example, data from Inspire and Uplift studies included direct comparisons of ICS+LABA versus LAMA and ICS+LABA versus ICS+LABA + LAMA, and an indirect comparison of LAMA versus ICS+LABA + LAMA. Utility values were derived from the EQ-5D using published literature as well as SGRQ scores which were then mapped to the EQ-5D. Costs included within the model were drug costs, acute COPD exacerbation costs (non-hospitalized and hospitalized exacerbation costs), and COPD maintenance costs (follow-up visits, additional medications and therapies) which were based on published sources.

Strengths of this analysis include that it considered final outcomes; mortality and treatment effect were modelled appropriately. As well, it considered the cost-effectiveness of monotherapy (LAMA), dual therapy and triple therapy. Furthermore, the study included a variety of sensitivity analyses, with appropriate distributions used to handle parameter uncertainty. Limitations of this analysis include that effectiveness data were derived from both direct and informal indirect comparisons using combinations of the three clinical trials rather than any attempt to synthesize the trial results in a formal manner. As a result, it was not possible to obtain consistent estimates for the cost effectiveness of ICS+LABA versus alternative treatments. Moreover, the analysis did not consider LABA as an alternative treatment.

In the base case analysis, only exacerbations varied between treatments. Using data from Inspire and Uplift trials, the incremental cost effectiveness ratio for ICS+LABA + LAMA versus ICS+LABA was £187,697/QALY and ICS+LABA was subject to extended dominance by ICS+LABA + LAMA and LAMA. Using data from Inspire and Optimal trials results were similar; the incremental cost effectiveness ratio for ICS+LABA + LAMA versus ICS+LABA was £93,737/QALY and ICS+LABA was subject to extended dominance by ICS+LABA + LAMA and LAMA. However, using data from Uplift and Optimal trials, the incremental cost effectiveness ratio for ICS+LABA + LAMA versus ICS+LABA was still high - £159,353/QALY. However in this instance, LAMA was subject to dominance by ICS+LABA. In sensitivity analyses, results were insensitive to time horizon and costs of non-hospitalized exacerbations, but sensitive to exacerbation rate (depending on source of data). In scenario based analysis, results were sensitive to scenarios including: treatment affects exacerbation and stable quality of life effects, and treatment affects exacerbation and mortality. Results were insensitive, however, to the addition of time horizon changes to the scenarios. At a threshold of £20,000/QALY, LAMA has the highest probability of being cost effective (using both data from Inspire and Uplift trials and data from Inspire and Optimal trials). However, using the Uplift and Optimal data, at a threshold of £20,000/QALY, ICS+LABA has the highest probability of being cost effective.

Although this study is independent from industry sponsorship, suggesting that the conclusion from this study may apply to Canada, its applicability may be limited given it is not from the Canadian perspective, it is of a limited time horizon (four years), and distinct COPD severity populations were not considered. Furthermore, the inconsistent results due to failure to pool the clinical trial results in a formal manner limit its usefulness.

Earnshaw et al. (2009)

Earnshaw and colleagues compared the cost effectiveness of ICS+LABA (fluticasone propionate 500 µg/salmeterol 50 µg), LABA (salmeterol 50 µg), ICS (fluticasone propionate 500 µg), and no maintenance (placebo) from a third-party US payer perspective.[6] Disease severity was defined using the American Thoracic Society criteria: COPD patients were classified as moderate to very severe. Disease progression based on decline in lung function and annual probability of mortality by disease severity were modelled. A treatment effect on both mortality and on exacerbation rates was assumed using hazard ratios of treatments compared to placebo from a single RCT.[15] Exacerbation rates were not assumed to vary by disease severity, nor was there an associated risk of mortality with exacerbations requiring hospitalization. The three year efficacy data from the clinical trial was extrapolated to a lifetime time horizon within the model. Costs included within the model were out patient physician visits, emergency department visits, laboratory tests, supplies, X-rays, additional treatments (antibiotics, corticosteroids) which were based on published literature and expert opinion.

The incremental cost effectiveness ratios for ICS+LABA versus placebo were $24,530/LY, $33,865/QALY, $11,405/exacerbation avoided, $23,456/hospital day avoided, and $61/symptom–free day gained. For ICS versus placebo, the incremental cost effectiveness ratios were $3,796/exacerbation avoided and $3,197/hospital day avoided. Placebo dominated ICS in terms of incremental cost per life gained, QALY gained, and symptom–free day gained. The incremental cost effectiveness ratios for LABA versus placebo were $15,098/LY, $20,797/QALY, $10,152/exacerbation avoided, $8,007/hospital day avoided, and $38/symptom–free day gained. However, ratios comparing active treatments were not presented and could not be inferred.

Strengths of the analysis include that final outcomes were considered and disease progression appeared to be modelled appropriately. However, effectiveness data were derived from a single study.

Applicability of this study is limited given that it is not an independent study, it is not from the Canadian perspective, distinct COPD severity populations were not considered, and results are not reported in a way to allow assessment of incremental cost effectiveness ratios.

Oba, 2009

Oba compared the cost effectiveness of ICS+LABA (salmeterol 50 µg / fluticasone propionate 500 µg), LABA (salmeterol 50 µg), ICS (fluticasone 500 µg) and placebo/no therapy from a US third party payer perspective.[4] Using the GOLD criteria, patients with moderate to very severe COPD were considered though no stratification by disease severity was undertaken. States related to the occurrence and absence of exacerbations and mortality – thus no modelling of COPD disease progression was incorporated. Transition probabilities for death and exacerbations were treatment specific with a cycle length of three months and a three year time horizon. Effectiveness data were derived from a single randomized controlled trial.[15] Utility values derived from SGRQ [25] and were mapped to the EQ-5D using an equation derived from a previous study by the same author.[26] Costs included within the model were drug acquisition costs (wholesale price, discounted by 15%, with a $2.50 dispensing fee), costs for

inpatient visit and emergency visit, and cost of antibiotic treatment which were based on published literature.

The incremental cost effectiveness ratio for ICS+LABA versus placebo/no therapy was $52,046/QALY, for LABA versus placebo was $56,519/QALY, and for ICS versus placebo/no therapy was $62,833/QALY. LABA and ICS monotherapies were subject to extended dominance by ICS+LABA compared to placebo/no therapy. In one-way deterministic analysis, results were sensitive to costs, all-cause mortality, hospitalization, and utility weights. Results from probabilistic analysis confirmed the findings of the deterministic analysis.

Strengths of this analysis include that it considered final outcomes (QALYs). The study had key weaknesses; effectiveness data were derived from a single study and information regarding parameter inputs was not reported transparently, therefore, making it difficult to assess how mortality and treatment effect were modelled.

Although this study was not financed by industry, applicability of this study is limited given that there is a lack of transparency in the reporting, it is not from the Canadian perspective, it is of a limited time horizon, distinct COPD severity populations were not considered, and COPD progression was not modelled.

Dal Negro et al. (2007)

Dal Negro and associates compared the cost effectiveness of ICS+LABA (salmeterol/fluticasone, formoterol/budesonide), LABA (salmeterol), ICS (fluticasone), placebo from an Italian societal perspective.[9] Using the GOLD criteria, the entire Italy COPD patient population entered the model. The average pulmonary capacity reduction of COPD patients and FEV_1 predicted values were used to calculate the probability of progression while the probability of death was calculated by applying stage-specific relative risk to mortality rates of the general population. Effectiveness data were derived from two published randomized controlled trials.[5,17] Outcome measures were numbers of exacerbations and symptom-free days. It was assumed treatment did not have an effect on FEV_1. Costs included within the model were drug acquisition costs, hospitalizations, medical visits examinations, oxygen therapy, lung ventilation, rehabilitation, and loss of productivity of patient and first degree relatives which were based on published literature.

All strategies dominated placebo/no therapy with the exception of ICS which was more costly. The incremental cost effectiveness ratio for ICS+LABA versus LABA (salmeterol/fluticasone) was €679.55/exacerbation and €3.31/symptom-free day and the incremental cost effectiveness ratio for ICS+LABA (formoterol/budesonide) versus LABA was €1,392.38/exacerbation and €3.48/symptom-free day. Results from the one-way deterministic analysis suggest that results were sensitive to treatment effect and costs. Although not presented in the reporting of the results, analysis suggests that formoterol/budesonide is subject to extended dominance through salmeterol/fluticasone and salmeterol alone.

The primary strength of the analysis was that treatment effect appeared to be modelled appropriately. The study had key weaknesses; effectiveness data were derived from only two randomized controlled trials and only intermediate outcomes were presented.

Applicability of this study is limited given that it is not an independent study, it is not from the Canadian perspective, only short term outcomes are presented and distinct COPD severity populations were not considered.

Gagnon et al. (2005)

Gagnon and colleagues compared the cost effectiveness of ICS+LABA, LABA, ICS, and comparison (no LABA or ICS, but other COPD treatment) from a third-party US payer perspective.[7] This study used effectiveness data derived from a published observational cohort study of treatment effectiveness.[13] The model assumed that treatment impacted mortality; no other treatment effects were considered. Using survival data in the form of records of death certificates, the three year efficacy data from the published observational cohort study was extrapolated to a lifetime time horizon using parametric survival models. Costs included within the model were outpatient prescription medications, ambulatory care (physician visits, radiology, laboratory testing, rehabilitation, and other outpatient procedures and services), and hospitalization.

Using a three year time horizon, LABA dominated ICS and comparison (no LABA or ICS) and the incremental cost effectiveness ratio for ICS+LABA versus LABA was $91,430/LY. Using a lifetime horizon, LABA dominated ICS, the incremental cost effectiveness ratio for LABA versus comparison (no LABA or ICS) was $6,110/LY and for ICS+LABA versus LABA was $27,570/LY. Sensitivity analysis included the use of the non-parametric bootstrap method which confirmed the results of the deterministic analysis.

Strengths of this analysis include that final outcomes were modelled and that treatment effect based on mortality was modelled appropriately in the short term analysis. However, effectiveness data were derived from observational data and the ability of this to provide true estimates of relative effectiveness may be limited and the use of parametric survival models to forecast long term survival in a chronic disease may be inappropriate. In addition, analysis did not consider the impact of COPD on quality of life which would likely lead to much higher incremental cost effectiveness ratios if results were presented as QALYs.

Applicability of this study is limited given that it is not an independent study, it is not from the Canadian perspective, distinct COPD severity populations were not considered, results were based on observational data, and the method for extrapolation may not have been appropriate.

Overall Conclusions

Overall, the studies identified in this review are of limited applicability to the current Canadian setting. Only two studies used effectiveness data from published network meta-analysis or mixed treatment comparison, one study used a published observational cohort study, and many used a single or selection

of randomized controlled trials. For some CUAs, non-utility measures were used to indirectly calculate QALYs for many of the cost-utility analyses. All but two studies are industry sponsored.

Only one Canadian study was found.[2] Its results suggest that ICS+LABA was more cost effective than LABA alone in patients with Stage 3 COPD (based on the American Thoracic Society criteria), though its cost effectiveness in patients with Stage 2 and Stage 1 was unclear. Despite some strengths, this study had limitations primarily relating to study sponsorship.

Of the non-Canadian studies, two were cost-effectiveness analyses, three were cost-utility analyses, and three were cost-effectiveness/utility analyses.

The studies conducted by NCGC[3] and Oba[4] were independent of manufacturer sponsorship. Both studies compare ICS+LABA to a variety of comparators. The population modelled in the analysis by NCGC was patients with severe to very severe COPD (based on the GOLD criteria) with a mean age of 66, while patients with moderate to very severe COPD (based on the GOLD criteria) with a mean age of 65 were modelled in the analysis by Oba. In both studies, the model had a limited time horizon (three and four year time frames).

The results of the NCGC report varied depending on the source of effectiveness data which limits its usefulness in decision making. The study by Oba which evaluated the cost effectiveness of ICS+LABA compared to monotherapies (LABA or ICS) and placebo only used effectiveness data derived from a single randomized controlled trial and the lack of transparency in reporting questions its applicability. Results from all manufacturer sponsored economic analyses favoured the manufacturer's treatment.

Overall, most studies compared ICS+LABA to placebo, LABA, and ICS, fewer studies examined the cost effectiveness of ICS+LABA versus LAMA, LAMA+LABA, and triple therapy (ICS+LABA + LAMA). Applicability of non-Canadian studies to any decision regarding the cost effectiveness of ICS+LABA is limited given they are not from the Canadian perspective; all except for two are industry sponsored and favour the manufacturer's therapy.

Overall Summary

In brief, nine economic analyses were identified; only one was Canadian. All but two economic analyses were financed by industry. The majority did not consider distinct COPD severity populations. Many reports used effectiveness data derived from a single randomized controlled trial. Some studies overestimated treatment effect by modelling effect on both FEV_1 and exacerbation. Certain studies reported results in a non-meaningful way.

Thus, given the contradictory results from the manufacturer sponsored studies and the independent studies and the consistent concerns over the quality and the relevance of the available studies, it is not possible to make any inferences on which if any patient population the use of ICS+LABA is cost effective.

Conclusions

In brief, this review highlights the paucity and the poor quality of current economic evidence for the cost effectiveness of ICS+LABA compared to single or combination therapies incorporating LABA, LAMA and ICS for chronic treatment of COPD.

Economic evidence for the cost effectiveness ICS+LABA compared to single or combination therapies incorporating LABA, LAMA and ICS for chronic treatment of COPD suggest that there are very few independent analyses; almost all studies are industry financed.

Given the contradictory results from the manufacturer sponsored studies and the independent studies and the consistent concerns over the quality and the relevance of the available studies, it is not possible to make any inferences on which if any patient population the use of ICS+LABA is cost effective.

To assist with the ODPRN review, an independent de novo economic model is required to address the cost effectiveness of ICS, LABA and LABA as single and combination therapies based on disease severity from the Canadian context. This model can then be used to assess the relative cost effectiveness of alternative reimbursement strategies relating to ICS+LABA.

Appendix A - Appendices
Appendix A1: Search Strategy

The following is the search strategy used in Medline (Ovid) and Embase.

Embase Classic+Embase (1946 to present (2013 December 04), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (1947 to 2013 December 03)

1. exp Pulmonary Disease, Chronic Obstructive/
2. exp Emphysema/ or exp Pulmonary Emphysema/
3. ((chronic adj2 obstructi*) and (pulmonary or airway* or air way* or lung$1 or airflow* or air flow*)).tw.
4. (COPD or COAD).tw.
5. (chronic adj2 bronchitis).tw.
6. emphysema*.tw.
7. or/1-6
8. Formoterol*.tw,rn.
9. (BD 40A or HSDB 7287 or Oxis or UNII-5ZZ84GCW8B).tw.
10. (eformoterol or Foradil).tw.
11. 73573-87-2.rn.
12. Indacaterol.tw,rn.
13. (Arcapta or Onbrez or QAB 149 or QAB149 or UNII-8OR09251MQ).tw.
14. 312753-06-3.rn.
15. Salmeterol*.tw,rn.
16. (Aeromax or Astmerole or "GR 33343 X" or "GR 33343X" or HSDB 7315 or SN408D or UNII-2I4BC502BT).tw.
17. 89365-50-4.rn.
18. Salmeterolxinafoate.tw,rn.
19. (Arial or Asmerole or Beglan or Betamican or Dilamax or Inaspir or Salmetedur or Serevent or Ultrabeta or UNII-6EW8Q962A5).tw.
20. 94749-08-3.rn.
21. ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (beta-agonist* or betaagonist* or beta-adrenergic* or adrenergic beta-receptor* or beta-receptor agonist* or beta-adrenoceptor agonist*)).tw.
22. ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (beta-2-agonist* or beta-2agonist* or beta-2-adrenergic* or adrenergic beta-2-receptor* or beta-2-receptor agonist* or beta-2-adrenoceptor agonist*)).tw.
23. ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (beta2-agonist* or beta2agonist* or beta2-adrenergic* or adrenergic beta2-receptor* or beta2-receptor agonist* or beta2- adrenoceptor agonist*)).tw.
24. ((longacting or long-acting) and ("beta(2)-agonist*" or "beta(2)agonist*" or "beta(2)-adrenergic*" or "adrenergic beta(2)-receptor*" or "beta(2)-receptor agonist*" or "beta(2)-adrenoceptor agonist*")).tw.

25. ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (B2-agonist* or B2-adrenergic* or adrenergic B2-receptor* or B2-receptor agonist* or B2-adrenoceptor agonist*)).tw.
26. ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (B-2-agonist* or B-2-adrenergic* or adrenergic B-2-receptor* or B-2-receptor agonist* or B-2-adrenoceptor agonist*)).tw.
27. (LABA or LABAs or Ultra-LABA* or UltraLABA*).tw.
28. ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and bronchodilator*).tw.
29. ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (betamimetic* or beta-mimetic*)).tw.
30. exp Adrenergic beta-Agonists/ or Bronchodilator Agents/
31. (longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting).tw.
32. 30 and 31
33. or/21-29,32
34. Administration, Inhalation/
35. exp Aerosols/
36. (inhal* or aerosol*).tw.
37. or/34-36
38. 33 and 37
39. or/8-20,38
40. Beclomethasone/
41. (Aerobec or AeroBec Forte or Aldecin or Apo-Beclomethasone or Ascocortonyl or AsmabecClickhaler).tw.
42. (Beclamet or Beclazone or BecloAsma or Beclo AZU or Beclocort or Becloforte or Beclomet or Beclometason* or Beclomethasone or Beclorhinol or Becloturmant or Beclovent or Becodisk* or Beconase or Becotide or BemedrexEasyhaler or Bronchocort).tw.
43. (Ecobec or Filair or Junik or Nasobec Aqueous or Prolair or Propaderm or Qvar or Respocort or Sanasthmax or Sanasthmyl or Vancenase or Vanceril or Ventolair or Viarin).tw.
44. (BMJ 5800 or EINECS 224-585-9 or UNII-KGZ1SLC28Z).tw.
45. 4419-39-0.rn.
46. Budesonide/
47. (Budesonide or Micronyl or Preferid or Pulmicort or Respules or Rhinocort or "S 1320" or Spirocort or Uceris or UNII-Q3OKS62Q6X).tw.
48. 51333-22-3.rn.
49. Fluticasone.tw,rn.
50. (Cutivate or Flixonase or Flixotide or Flonase or Flovent or Fluticason* or HSDB 7740 or UNII-CUT2W21N7U).tw.
51. Glucocorticoids/
52. glucocorticoid*.tw.
53. Adrenal Cortex Hormones/

54. (corticoid* or corticosteroid* or cortico-steroid*).tw.
55. ((adrenal cortex or adrenal cortical) adj3 hormon*).tw.
56. ((adrenal cortex or adrenal cortical) adj3 steroid*).tw.
57. or/51-56
58. 57 and 37
59. or/40-50,58
60. (Fluticasone adj3 salmeterol).tw,rn.
61. (Adoair or Advair or Foxair or "Quikhale SF" or Seretide or Viani).tw.
62. (formoterol adj3 mometasone).tw,rn.
63. (Zenhale or Dulera).tw.
64. (formoterol adj3 budesonide).tw,rn.
65. (Rilast or Symbicord or Symbicort or Vannair).tw.
66. (vilanterol adj3 fluticasone).tw,rn.
67. Breo Ellipta.tw.
68. or/60-67
69. tiotropium.tw,rn.
70. (BA 679 BR or BA 679BR or Spiriva or tiotropium or UNII-0EB439235F or UNII-XX112XZP0J).tw.
71. aclidiniumbromide.tw,rn.
72. (LAS 34273 or LAS W-330 or BretarisGenuair or EkliraGenuair or TudorzaPressair or UNII-UQW7UF9N91).tw.
73. glycoyrroniumbromide.tw,rn.
74. (erythro-glycopyrronium bromide or UNII-9SFK0PX55W).tw.
75. ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (anticholinergic* or anti-cholinergic* or cholinolytic* or cholinergic-blocking or antimuscarinic* or anti-muscarinic* or ((cholinergic or acetylcholine or muscarinic) adj3 antagonist*))).tw.
76. (LAMA or LAMAs or Ultra-LAMA* or UltraLAMA*).tw.
77. Muscarinic Antagonists/ or Cholinergic Antagonists/
78. 77 and 31
79. 75 or 76 or 78
80. 79 and 37
81. or/69-74,80
82. 39 or 59 or 68 or 81
83. 7 and 82
84. health economics/
85. exp economic evaluation/
86. exp "health care cost"/
87. exp pharmacoeconomics/
88. 84 or 85 or 86 or 87
89. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
90. (expenditure$ not energy).ti,ab.

91. (value adj2 money).ti,ab.
92. budget$.ti,ab.
93. 89 or 90 or 91 or 92
94. 88 or 93
95. Economics/
96. exp "Costs and Cost Analysis"/
97. "Value of Life"/
98. exp Economics, Hospital/
99. Economics, Medical/
100. Economics, Nursing/
101. Economics, Pharmaceutical/
102. 95 or 96 or 97 or 98 or 99 or 100 or 101
103. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
104. (expenditure$ not energy).ti,ab.
105. (value adj1 money).ti,ab.
106. budget$.ti,ab.
107. 103 or 104 or 105 or 106
108. 102 or 107
109. 94 or 108
110. 83 and 109
111. remove duplicates from 110

Appendix A2: List of Citations Included by Manufacturer

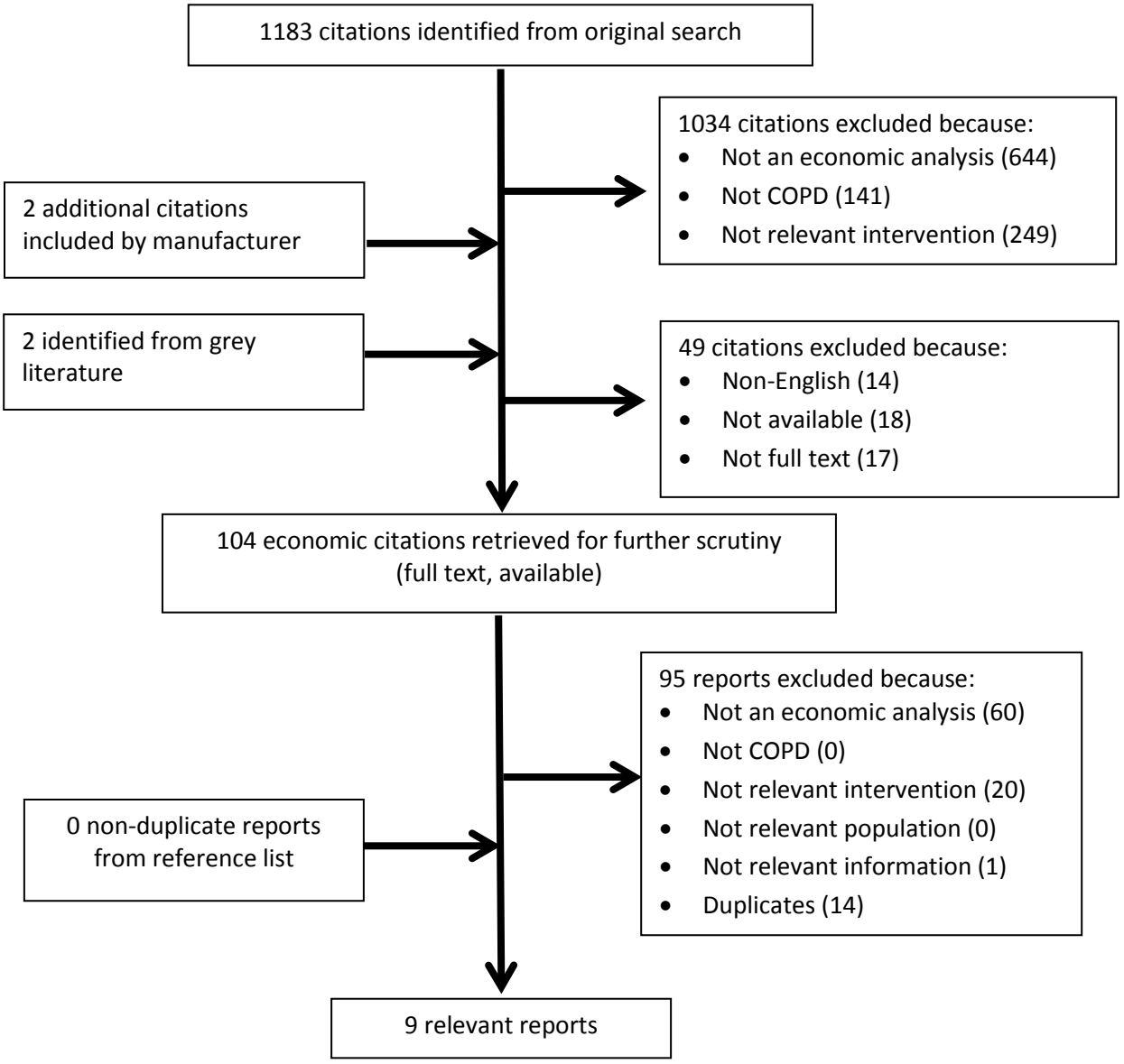
The following table lists studies which were included by the manufacturer in their evidence submission package.

Reference #	Study Reference	Additional Citation From Original Search	Relevant Citation	Reason For Inclusion/Exclusion
[27]	AbuDagga A, et al. Exacerbations among chronic bronchitis patients treated with maintenance medications from a US managed care population: An administrative claims data analysis. International Journal of COPD 2013;8:175-85.	Yes	No	Results are reported as mean cost per exacerbation in terms of all COPD patients as well as COPD severity, not as an incremental cost per outcome relative to a treatment. Therefore, this article is not considered an economic analysis
[28]	AbuDagga A, et al. Healthcare utilization and costs among chronic bronchitis patients treated with maintenance medications from a US managed care population. Journal of Medical Economics 2013;16(3):421-9.	Yes	No	Results are reported as mean COPD-related total costs and mean follow-up COPD-related costs, not as an incremental cost per outcome relative to a treatment. Therefore, this article is not considered an economic analysis
[29]	Mittmann N, et al. Cost effectiveness of budesonide/formoterol added to tiotropium bromide versus placebo added to tiotropium bromide in patients with chronic obstructive pulmonary disease: Australian, Canadian and Swedish healthcare perspectives. Pharmacoeconomics 2011;29(5):403-14.	No	No	This article compares ICS+LABA + LAMA versus LAMA + Placebo. Therefore, it is not a relevant article since it is not a relevant comparison. Relevant comparisons include ICS+LABA in comparison to LABA, ICS, LAMA and any combination of the above.

Reference #	Study Reference	Additional Citation From Original Search	Relevant Citation	Reason For Inclusion/Exclusion
30	Nielsen R, et al. Cost effectiveness of adding budesonide/formoterol to tiotropium in COPD in four Nordic countries. Respir Med 2013;107(11):1709-21.	No	No	This article compares ICS+LABA + LAMA versus LAMA + Placebo. Therefore, it is not a relevant article since it is not a relevant comparison. Relevant comparisons include ICS+LABA in comparison to LABA, ICS, LAMA and any combination of the above.
31	Risebrough N, et al. Roflumilast (DAXAS) for the treatment of COPD in Canada: value for money? [abstract]. Can Respir J 2011;18(Suppl A):11A.	No	No	This article compares a phosphodiesterase type 4 inhibitor (roflumilast) plus LAMA versus LAMA alone and LAMA+ICS+LABA which is not a relevant comparison. Relevant comparisons include ICS+LABA in comparison to LABA, ICS, LAMA and any combination of the above. As well, this article is only available in abstract form.
32	Zafari Z, et al. Impact of multiple treatment comparison meta-analysis on value of information evaluations: a case study of pharmacotherapies for chronic obstructive pulmonary diseases [abstract]. Value in Health 2013;16(3):A26-7.	No	No	Although this article considers the appropriate comparators, it is only available in abstract form. It is, therefore, excluded.

Appendix A3: Results of Search

The following illustrates the selected studies for the review.



Appendix A4: List of Excluded Studies

The following table lists the studies excluded from the review in addition to the rationale for their exclusion.

Reference #	Study Reference	Reason For Exclusion
[33]	Dalal AA, St CM, Petersen HV, Roberts MH, Blanchette CM, Manavi-Zieverink K. Cost-effectiveness of combination fluticasone propionate-salmeterol 250/50 microg versus salmeterol in severe COPD patients. International journal of chronic obstructive pulmonary disease. 2010;5:179-87.	Not economic analysis
[34]	Dalal AA, St CM, Petersen HV, Roberts MH, Blanchette CM, Manavi-Zieverink K. Cost-effectiveness of combination fluticasone propionate-salmeterol 250/50 microg versus salmeterol in severe COPD patients. Int J Chron Obstruct Pulmon Dis. 2010;5:179-87. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921685	Not economic analysis
[35]	Dalal AA, Roberts MH, Petersen HV, Blanchette CM, Mapel DW. Comparative cost-effectiveness of a fluticasone-propionate/salmeterol combination versus anticholinergics as initial maintenance therapy for chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2011;6:13-22. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3034283	Not economic analysis
[36]	Dalal AA, Shah M, D'souza A, Mapel DW. Outcomes post-hospitalization or following an emergency department visit related to chronic obstructive pulmonary disease (COPD): Data from administrative claims [abstract]. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS 2010 New Orleans, LA United States Conference. 2010.	Not economic analysis
[37]	Roberts M, Mapel D, Petersen H, Blanchette C, Ramachandran S. Comparative effectiveness of budesonide/formoterol and fluticasone/salmeterol for COPD management. J Med Econ. 2011;14(6):769-76.	Not economic analysis
[38]	Alifano M, Cuvelier A, Delage A, Roche N, Lamia B, Molano LC, et al. Treatment of COPD: From pharmacological to instrumental therapies. European Respiratory Review. 2010;19(115):7-23.	Not economic analysis
[39]	Bryan J. Novel inhaler devices: Balancing innovation against price is important. Pharmaceutical Journal. 2005;274(7338):241-2.	Not economic analysis
[40]	Cazzola M, Matera MG. Long-Acting Bronchodilators Are the First-Choice Option for the Treatment of Stable COPD. Chest. 2004;125(1):9-11.	Not economic analysis
[41]	Cao Z, Zou KH, Baker CL, Su J, Paulose-Ram R, Durden E, et al. Respiratory-related medical expenditure and inpatient utilisation among COPD patients receiving long-acting bronchodilator therapy. Journal of Medical Economics. 2011;14(2):147-58.	Not economic analysis
[42]	Cooper CB, Tashkin DP. Recent developments in inhaled therapy in stable chronic obstructive pulmonary disease. British Medical Journal. 2005;330(7492):640-4.	Not economic analysis

Reference #	Study Reference	Reason For Exclusion
43	Dalal AA, Petersen H, Simoni-Wastila L, Blanchette CM. Healthcare costs associated with initial maintenance therapy with fluticasone propionate 250 mug/salmeterol 50 mug combination versus anticholinergic bronchodilators in elderly US Medicare-eligible beneficiaries with COPD. Journal of Medical Economics. 2009;12(4):339-47.	Not economic analysis
44	Dalal AA. Cost-effectiveness of combination fluticasone propionate/salmeterol 250/50 mcg versus salmeterol in chronic obstructive pulmonary disease (COPD): Data from two well controlled exacerbation trials [abstract]. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference. 2010.	Not economic analysis
45	Dalal AA, Roberts MH, Petersen HV, Blanchette CM, Mapel DW. Comparative cost-effectiveness of a futicasone-propionate/salmeterol combination versus anticholinergics as initial maintenance therapy for chronic obstructive pulmonary disease. International Journal of COPD. 2011;6(1):13-22.	Not economic analysis
46	Dalal AA, Shah M, D'Souza AO, Mapel DW. COPD-related healthcare utilization and costs after discharge from a hospitalization or emergency department visit on a regimen of fluticasone propionate-salmeterol combination versus other maintenance therapies. American Journal of Managed Care. 2011;17(3):e55-e65.	Not economic analysis
47	Dalal AA, Candrilli SD, Davis KL. Outcomes and costs associated with initial maintenance therapy with fluticasone propionate-salmeterol xinafoate 250 microg/50 microg combination versus tiotropium in commercially insured patients with COPD. Managed care. 2011;20(8):46-55.	Not economic analysis
48	De BW. Inhaled salmeterol/fluticasone propionate combination in chronic obstructive pulmonary disease. American Journal of Respiratory Medicine. 2002;1(4):283.	Not economic analysis
49	Faulkner MA, Hilleman DE. The economic impact of chronic obstructive pulmonary disease. Expert Opinion on Pharmacotherapy. 2002;3(3):219-28.	Not economic analysis
50	Fishman AP. One hundred years of chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 2005;171(9):941-8.	Not economic analysis
51	Patients with severe COPD may benefit from the addition of an inhaled corticosteroid. Formulary. 2007;42(3):178-83.	Not economic analysis
52	Friedman M, Menjoge SS, Anton SF, Kesten S. Healthcare costs with tiotropium plus usual care versus usual care alone following 1 year of treatment in patients with Chronic Obstructive Pulmonary Disorder (COPD). Pharmacoeconomics. 2004;22(11):741-9.	Not economic analysis
53	Frith P, McKenzie D, Pierce R. Management of chronic obstructive pulmonary disease in the twenty-first century. Internal Medicine Journal. 2001;31(9):508-11.	Not economic analysis

Reference #	Study Reference	Reason For Exclusion
54	Gross NJ. The COPD pipeline II. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2010;7(1):76-8.	Not economic analysis
55	Gross N. The COPD pipeline V. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2010;7(4):307-9.	Not economic analysis
56	Gross NJ. The COPD pipeline VIII. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2011;8(1):52-4.	Not economic analysis
57	Gross NJ. The COPD pipeline X. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2011;8(3):244-7.	Not economic analysis
58	Gross NJ, Hanania NA. The COPD pipeline XII. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2011;8(5):387-91.	Not economic analysis
59	Guarascio AJ, Ray SM, Finch CK, Self TH. The clinical and economic burden of chronic obstructive pulmonary disease in the USA. ClinicoEconomics and Outcomes Research. 2013;5(1):235-45.	Not economic analysis
60	Halpern R, Baker CL, Su J, Woodruff KB, Paulose-Ram R, Porter V, et al. Outcomes associated with initiation of tiotropium or fluticasone/salmeterol in patients with chronic obstructive pulmonary disease. Patient Preference and Adherence. 2011;5:375-88.	Not economic analysis
61	Herrick TM, Million RP. Tapping the potential of fixed-dose combinations. Nature Reviews Drug Discovery. 2007;6(7):513-4.	Not economic analysis
62	Izquierdo-Alonso JL, de Miguel-Diez J. Economic impact of pulmonary drugs on direct costs of stable chronic obstructive pulmonary disease. COPD. 2004;1(2):215-23.	Not economic analysis
63	Jones D. Long-acting inhaled bronchodilators for COPD - Lack of logic continues. New Zealand Medical Journal. 2005;118(1222):U1669.	Not economic analysis
64	Jones D. Long-acting inhaled bronchodilators for COPD--lack of logic continues. The New Zealand medical journal. 2005;118(1222):U1669.	Not economic analysis
65	Kardos P, Wencker M, Glaab T, Vogelmeier C. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 2007;175(2):144-9.	Not economic analysis
66	Kozma CM, Paris AL, Plauschinat CA, Slaton T, Mackowiak JI. Comparison of resource use by COPD patients on inhaled therapies with long-acting bronchodilators: a database study. BMC pulmonary medicine. 2011;11:61.	Not economic analysis
67	Kozma CM, Paris AL, Plauschinat CA, Slaton T, Mackowiak JI. Comparison of resource use by COPD patients on inhaled therapies with long-acting bronchodilators: A database study. BMC pulmonary medicine. 2011;11:61.	Not economic analysis
68	Kramer JM. Balancing the benefits and risks of inhaled long-acting beta-agonists - The influence of values. New England Journal of Medicine. 2009;360(16):1592-5.	Not economic analysis
69	Lee TA, Weiss KB, Sullivan SD, Sin DD, Golmohammadi K, Jacobs P. Cost-effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease (multiple letters). American Journal of Medicine. 2004;117(8):618-9.	Not economic analysis

Reference #	Study Reference	Reason For Exclusion
[70]	Mapel DW, Hurley JS, Dalal AA, Blanchette CM. The role of combination inhaled corticosteroid/long-acting beta-agonist therapy in COPD management. Primary Care Respiratory Journal. 2010;19(2):93-103.	Not economic analysis
[71]	Mapel DW, Roberts MH. New Clinical insights into chronic obstructive pulmonary disease and their implications for pharmacoeconomic analyses. Pharmacoeconomics. 2012;30(10):869-85.	Not economic analysis
[72]	Molken MRV, Lee TA. Economic modeling in chronic obstructive pulmonary disease. Proceedings of the American Thoracic Society. 2006;3(7):630-4.	Not economic analysis
[73]	Morjaria JB, Morice HA. Fluticasone furoate and vilanterol for COPD. The Lancet Respiratory Medicine. 2013;1(5):e21.	Not economic analysis
[74]	Dal Negro WR, Bonadiman L, Turati C, Turco P. Clinical and pharmacoeconomic profile of COPD patients with FEV1 50-60% predicted: Pilot study on the impact of the extended indication of ICS+LABA. Therapeutic Advances in Respiratory Disease. 2009;3(2):51-8.	Not economic analysis
[75]	Pingleton SK. Pulmonary medicine. Journal of the American Medical Association. 1996;275(23):1849-50.	Not economic analysis
[76]	Rascati KL, Akazawa M, Johnsrud M, Stanford RH, Blanchette CM. Comparison of hospitalizations, emergency department visits, and costs in a historical cohort of Texas Medicaid patients with chronic obstructive pulmonary disease, by initial medication regimen. Clinical Therapeutics. 2007;29(6):1203-13.	Not economic analysis
[77]	Rich A. Corticosteroids and chronic obstructive pulmonary disease in the Nursing Home. Journal of the American Medical Directors Association. 2005;6(3 Suppl):S67-S74.	Not economic analysis
[78]	Roberts M, Mapel D, Petersen H, Blanchette C, Ramachandran S. Comparative effectiveness of budesonide/formoterol and fluticasone/ salmeterol for COPD management. Journal of Medical Economics. 2011;14(6):769-76.	Not economic analysis
[79]	Roberts MH, Dalal AA. Clinical and economic outcomes in an observational study of COPD maintenance therapies: Multivariable regression versus propensity score matching. International Journal of COPD. 2012;7:221-33.	Not economic analysis
[80]	Rogol PR, Hahn DL, Kerstjens HAM, Brand PLP, Postma DS. Bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airways disease. New England Journal of Medicine. 1993;328(14):1044-5.	Not economic analysis
[81]	Saha S, Siva R, Brightling CE, Pavord ID. COPD: An inhaled corticosteroid-resistant, oral corticosteroid-responsive condition. European Respiratory Journal. 2006;27(4):863-5.	Not economic analysis
[82]	Shaya FT, El Khoury AC, Samant ND, Scharf SM. Utilization of health care resources in a high-risk medicaid population with chronic obstructive pulmonary disease. P and T. 2006;31(5):261-8.	Not economic analysis

Reference #	Study Reference	Reason For Exclusion
[83]	Simoni-Wastila L, Blanchette CM, Qian J, Yang H, Zhao L, Zuckerman IH, et al. Burden of chronic obstructive pulmonary disease in medicare beneficiaries residing in long-term care facilities. American Journal Geriatric Pharmacotherapy. 2009;7(5):262-70.	Not economic analysis
[84]	Sullivan SD, Briggs A. Improving survival in chronic obstructive pulmonary disease: Assessing the value of life-saving therapy. Proceedings of the American Thoracic Society. 2006;3(7):617-8.	Not economic analysis
[85]	Thirstrup S, Kampmann JP, MacAllister R, Vassiliou V, Hyde C, Dretzke J, et al. Combined salmeterol and fluticasone for COPD (multiple letters). Lancet. 2003;361(9369):1650-3.	Not economic analysis
[86]	van Arnum P. Zone in on: Drug spending: Generic-drug incursion and reduced demand contribute to modest gains. Pharmaceutical Technology. 2012;36(5):26.	Not economic analysis
[87]	Varkey B. Weighing the benefits and risks of inhaled corticosteroids. Current Opinion in Pulmonary Medicine. 2007;13(2):89.	Not economic analysis
[88]	Vestbo J. Choice of medications when treating stable COPD. Clinical Respiratory Journal. 2010;4(4):195-6.	Not economic analysis
[89]	White P. COPD in primary care: A time of opportunity. British Journal of General Practice. 2010;60(576):477-8.	Not economic analysis
[90]	Yu AP, Guerin A, De Leon DP, Ramakrishnan K, Wu EQ, Mocarski M, et al. Clinical and economic outcomes of multiple versus single long-acting inhalers in COPD. Respiratory Medicine. 2011;105(12):1861-71.	Not economic analysis
[91]	Borg S, Ericsson A, Wedzicha J, Gulsvik A, Lundback B, Donaldson GC, et al. A computer simulation model of the natural history and economic impact of chronic obstructive pulmonary disease. Value Health. 2004 Mar;7(2):153-67.	Not relevant intervention
[92]	Spencer M, Briggs AH, Grossman RF, Rance L. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. Pharmacoeconomics. 2005;23(6):619-37.	Not relevant intervention
[93]	Chandra K, Blackhouse G, McCurdy BR, Bornstein M, Campbell K, Costa V, et al. Cost-effectiveness of interventions for chronic obstructive pulmonary disease (COPD) using an Ontario policy model. Ont Health Technol Assess Ser. 2012;12(12):1-61. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3384363	Not relevant intervention
[94]	Lee KH, Phua J, Lim TK. Evaluating the pharmacoeconomic effect of adding tiotropium bromide to the management of chronic obstructive pulmonary disease patients in Singapore. Respir Med. 2006 Dec;100(12):2190-6.	Not relevant intervention
[95]	Najafzadeh M, Marra CA, Sadatsafavi M, Aaron SD, Sullivan SD, Vandemheen KL, et al. Cost effectiveness of therapy with combinations of long acting bronchodilators and inhaled steroids for treatment of COPD. Thorax. 2008 Nov;63(11):962-7.	Not relevant intervention
[96]	Gaebel K, Blackhouse G, Robertson D, Xie F, Assasi N, McIvor A, et al. Triple Therapy for Moderate-to-Severe Chronic Obstructive Pulmonary	Not relevant intervention

Reference #	Study Reference	Reason For Exclusion
	Disease. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2010 May. [cited 2013 Dec 3]. Available from: http://www.cadth.ca/index.php/en/hta/reports-publications/search/publication/1690	
97	Akazawa M, Hayflinger DC, Stanford RH, Blanchette CM. Economic assessment of initial maintenance therapy for chronic obstructive pulmonary disease. American Journal of Managed Care. 2008;14(7):438-48.	Not relevant intervention
98	Dalal AA, Shah MB, D'Souza AO, Lunacsek OE, Nagar SP, Crater GD. Observational study of the outcomes and costs of initiating maintenance therapies in patients with moderate exacerbations of COPD. Respiratory research. 2012;13:41.	Not relevant intervention
99	Dalal AA, Shah MB, D'Souza AO, Lunacsek OE, Nagar SP, Crater GD. Observational study of the outcomes and costs of initiating maintenance therapies in patients with moderate exacerbations of COPD. Respiratory research. 2012;13:41.	Not relevant intervention
100	Hettle R, Wouters H, Ayres J, Gani R, Kelly S, Lion M, et al. Cost-utility analysis of tiotropium versus usual care in patients with COPD in the UK and Belgium. Respiratory Medicine. 2012;106(12):1722-33.	Not relevant intervention
101	Jones PW, Wilson K, Sondhi S. Cost-effectiveness of salmeterol in patients with chronic obstructive pulmonary disease: An economic evaluation. Respiratory Medicine. 2003;97(1):20-6.	Not relevant intervention
102	Lee K-H, Phua J, Lim T-K. Evaluating the pharmacoeconomic effect of adding tiotropium bromide to the management of chronic obstructive pulmonary disease patients in Singapore. Respiratory Medicine. 2006;100(12):2190-6.	Not relevant intervention
103	Mapel DW, Schum M, Lydick E, Marton JP. A new method for examining the cost savings of reducing COPD exacerbations. Pharmacoeconomics. 2010;28(9):733-49.	Not relevant intervention
104	Miravitlles M, Brosa M, Velasco M, Crespo C, Gobartt E, Diaz S, et al. An economic analysis of pharmacological treatment of COPD in Spain. Respiratory Medicine. 2009;103(5):714-21.	Not relevant intervention
105	Dal NR, Bonadiman L, Tognella S, Micheletto C, Turco P. The impact of LABA+ICS fixed combinations on morbidity and economic burden of COPD in Italy: A six-year observational study. Therapeutic Advances in Respiratory Disease. 2011;5(2):83-90.	Not relevant intervention
30	Nielsen R, Kankaanranta H, Bjermer L, Lange P, Arnetorp S, Hedegaard M, et al. Cost effectiveness of adding budesonide/formoterol to tiotropium in COPD in four Nordic countries. Respiratory Medicine. 2013;107(11):1709-21.	Not relevant intervention
106	Oostenbrink JB, Al MJ, Oppe M, Rutten-Van Molken MPMH. Expected value of perfect information: An empirical example of reducing decision uncertainty by conducting additional research. Value in Health. 2008;11(7):1070-80.	Not relevant intervention

Reference #	Study Reference	Reason For Exclusion
107	Sin DD, Golmohammadi K, Jacobs P. Cost-effectiveness of inhaled corticosteroids for chronic obstructive pulmonary disease according to disease severity. American Journal of Medicine. 2004;116(5):325-31.	Not relevant intervention
108	Spencer M, Briggs AH, Grossman RF, Rance L. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. Pharmacoeconomics. 2005;23(6):619-37.	Not relevant intervention
109	Zaniolo O, Iannazzo S, Pradelli L, Miravitlles M. Pharmacoeconomic evaluation of tiotropium bromide in the long-term treatment of chronic obstructive pulmonary disease (COPD) in Italy. European Journal of Health Economics. 2012;13(1):71-80.	Not relevant intervention
110	Lofdahl CG, Ericsson A, Svensson K, Andreasson E. Cost effectiveness of budesonide/formoterol in a single inhaler for COPD compared with each monocomponent used alone. Pharmacoeconomics. 2005;23(4):365-75.	Not relevant information
111	Briggs AH, Glick HA, Lozano-Ortega G, Spencer M, Calverley PM, Jones PW, et al. Is treatment with ICS and LABA cost-effective for COPD? Multinational economic analysis of the TORCH study. Eur Respir J. 2010 Mar;35(3):532-9.	Duplicate
112	Briggs AH, Glick HA, Lozano-Ortega G, Spencer M, Calverley PMA, Jones PW, et al. Is treatment with ICS and LABA cost-effective for COPD? Multinational economic analysis of the TORCH study. European Respiratory Journal. 2010;35(3):532-9.	Duplicate
113	Chuck A, Jacobs P, Mayers I, Marciniuk D. Cost-effectiveness of combination therapy for chronic obstructive pulmonary disease. Can Respir J. 2008 Nov;15(8):437-43. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2682167	Duplicate
114	Chuck A, Jacobs P, Mayers I, Marciniuk D. Cost-effectiveness of combination therapy for chronic obstructive pulmonary disease. Canadian respiratory journal : journal of the Canadian Thoracic Society. 2008;15(8):437-43.	Duplicate
115	Earnshaw SR, Wilson MR, Dalal AA, Chambers MG, Jhingran P, Stanford R, et al. Cost-effectiveness of fluticasone propionate/salmeterol (500/50 microg) in the treatment of COPD. Respir Med. 2009 Jan;103(1):12-21.	Duplicate
116	Earnshaw SR, Wilson MR, Dalal AA, Chambers MG, Jhingran P, Stanford R, et al. Cost-effectiveness of fluticasone propionate/salmeterol (500/50 mug) in the treatment of COPD. Respiratory Medicine. 2009;103(1):12-21.	Duplicate
117	Gagnon YM, Levy AR, Spencer MD, Hurley JS, Frost FJ, Mapel DW, et al. Economic evaluation of treating chronic obstructive pulmonary disease with inhaled corticosteroids and long-acting beta2-agonists in a health maintenance organization. Respiratory Medicine. 2005;99(12):1534-45.	Duplicate

Reference #	Study Reference	Reason For Exclusion
118	Hertel N, Kotchie RW, Samyshkin Y, Radford M, Humphreys S, Jameson K. Cost-effectiveness of available treatment options for patients suffering from severe COPD in the UK: a fully incremental analysis. Int J Chron Obstruct Pulmon Dis. 2012;7:183-99. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3325000	Duplicate
119	Hertel N, Kotchie RW, Samyshkin Y, Radford M, Humphreys S, Jameson K. Cost-effectiveness of available treatment options for patients suffering from severe COPD in the UK: A fully incremental analysis. International Journal of COPD. 2012;7:183-99.	Duplicate
120	Lofdahl C-G, Ericsson A, Svensson K, Andreasson E. Cost effectiveness of budesonide/formoterol in a single inhaler for COPD compared with each monocomponent used alone. Pharmacoeconomics. 2005;23(4):365-75.	Duplicate
121	Dal NR, Eandi M, Pradelli L, Iannazzo S. Cost-effectiveness and healthcare budget impact in Italy of inhaled corticosteroids and brochodilators for severe and very severe COPD patients. International Journal of COPD. 2007;2(2):169-76.	Duplicate
122	Oba Y. Cost-effectiveness of salmeterol, fluticasone, and combination therapy for COPD. Am J Manag Care. 2009 Apr;15(4):226-32.	Duplicate
123	Oba Y. Cost-effectiveness of salmeterol, fluticasone, and combination therapy for COPD. The American journal of managed care. 2009;15(4):226-32.	Duplicate
124	Oba Y. Cost-Effectiveness of salmeterol, fluticasone, and combination therapy for COPD. American Journal of Managed Care. 2009;15(4):225-32.	Duplicate

Appendix A5: List of Included Studies

The following table lists the studies included within the review.

Reference #	Study Reference
[11]	Briggs AH, Glick HA, Lozano-Ortega G, Spencer M, Calverley PM, Jones PW, et al. Is treatment with ICS and LABA cost-effective for COPD? Multinational economic analysis of the TORCH study. Eur Respir J. 2010 Mar;35(3):532-9.
[2]	Chuck A, Jacobs P, Mayers I, Marciniuk D. Cost-effectiveness of combination therapy for chronic obstructive pulmonary disease. Can Respir J. 2008 Nov;15(8):437-43. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2682167
[6]	Earnshaw SR, Wilson MR, Dalal AA, Chambers MG, Jhingran P, Stanford R, et al. Cost-effectiveness of fluticasone propionate/salmeterol (500/50 microg) in the treatment of COPD. Respir Med. 2009 Jan;103(1):12-21.
[7]	Gagnon YM, Levy AR, Spencer MD, Hurley JS, Frost FJ, Mapel DW, et al. Economic evaluation of treating chronic obstructive pulmonary disease with inhaled corticosteroids and long-acting beta2-agonists in a health maintenance organization. Respir Med. 2005 Dec;99(12):1534-45.
[10]	Guillermo AJ, Thuresson P-O, Machnicki G, Mungapen L, Kraemer M, Asukai Y, et al. The Cost-Effectiveness and Budget Impact of Introducing Indacaterol into the Colombian Health System. Value in Health Regional Issues. 1(2):165-71.
[8]	Hertel N, Kotchie RW, Samyshkin Y, Radford M, Humphreys S, Jameson K. Cost-effectiveness of available treatment options for patients suffering from severe COPD in the UK: a fully incremental analysis. Int J Chron Obstruct Pulmon Dis. 2012;7:183-99. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3325000
[3]	National Clinical Guideline Centre. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Clinical Guideline Centre; 2010 Jun. [cited 2013 Dec 3]. Available from: http://guidance.nice.org.uk/CG101/Guidance/pdf/English
[9]	Dal NR, Eandi M, Pradelli L, Iannazzo S. Cost-effectiveness and healthcare budget impact in Italy of inhaled corticosteroids and bronchodilators for severe and very severe COPD patients. Int J Chron Obstruct Pulmon Dis. 2007;2(2):169-76. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2695615
[4]	Oba Y. Cost-effectiveness of salmeterol, fluticasone, and combination therapy for COPD. Am J Manag Care. 2009 Apr;15(4):226-32.

Appendix A6: Characteristics of Reviewed Studies

Study	Chuck et al., 2008
Sponsorship	GlaxoSmithKline
Country	Canada
Perspective	Health systems perspective
Study type	CUA
Comparators	LABA [Oxeze (formoterol 12 µg), Serevent (salmeterol 50 µg)] ICS+LABA [Advair (salmeterol 50 µg/fluticasone propionate 250 µg, (salmeterol 50 µg/fluticasone propionate 500 µg), Symbicort (budesonide 200 µg/ formoterol 6 µg]
Populations	COPD patients with Stage 1 ($FEV_1 \geq 50\%$ of predicted), Stage 2 (FEV_1 35%-49.9% predicted) or Stage 3 ($FEV_1 < 35\%$ predicted) disease based on the American Thoracic Society criteria Mean age of 61 years
Time horizon	3 years Lifetime
Type of model	Markov
Cycle length	3 months
Efficacy inputs	Exacerbations
Adverse events	Not included
Utilities	EQ-5D
Discounting	Costs and outcomes at 3%
Outcomes	Incremental cost per QALY
Results	<u>3 year time horizon</u> ICUR for ICS+LABA (Stage 3) versus LABA is $39,000/QALY ICUR for ICS+LABA (Stage 2 and 3) versus LABA is $47,500/QALY ICUR for ICS+LABA (all Stages) versus LABA is $450,333/QALY <u>Lifetime horizon</u> ICUR for ICS+LABA (Stage 3) versus LABA is $25,333/QALY ICUR for ICS+LABA (Stage 2 and 3) versus LABA is $50,571/QALY ICUR for ICS+LABA (all Stages) versus LABA is $448,571/QALY
Types of sensitivity analysis	<u>Deterministic analysis (one way)</u> Relative risk in all-cause mortality <u>Deterministic analysis (scenario)</u> Exclusion of TORCH study in relative risk reduction <u>Probabilistic analysis (Monte Carlo simulation)</u> Treatment effect, utilities, costs, transition probability (triangular distribution)

Study	Chuck et al., 2008
Sensitivity analysis results	Deterministic analysis (one way) Results insensitive to relative risk in all-cause mortality Deterministic analysis (scenario) Results insensitive to exclusion of TORCH study in relative risk reduction Probabilistic analysis (Monte Carlo simulation) At a threshold of $50,000/QALY, the probability of ICS+LABA (for Stage 3) being more cost effective than LABA alone is 80%, the probability of ICS+LABA (for Stage2 and 3) being more cost effective than LABA alone is 55%, ICS+LABA (for all Stages) was never more cost effective than LABA alone Results are similar for both time horizons
Points to consider	Costs CDN$ (2005/06) Efficacy data from systematic review of four clinical trials The analysis reports three separate groups: ICS+LABA for Stage 3, ICS+LABA for Stage 2 and 3, and ICS+LABA for all Stages (1-3) compared to LABA alone (for all Stages) Adverse events not included Utilities derived from the EQ-5D Distinct COPD severity population modelled In probabilistic analysis, all parameter inputs assumed a triangular distribution Comparison of monotherapy (LABA), dual therapy (ICS+LABA)

Study	Guillermo Ariza et al., 2012
Sponsorship	Novartis
Country	Colombia
Perspective	Health care payer perspective
Study type	CEA/CUA
Comparators	LABA [Onbrez Breezhaler (indacaterol)] ICS+LABA [Seretide (salmeterol/fluticasone) ICS+LABA [Symbicort (formoterol/budesonide)] LAMA [Spiriva (tiotropium)]
Population	Patients with COPD with mild-very severe based on the GOLD criteria Age not specified
Time horizon	5 year
Type of model	Markov
Cycle length	3 months
Efficacy inputs	FEV_1 Exacerbation
Adverse events	Not included
Utilities	EQ-5D
Discounting	Costs and outcomes at 5%
Outcomes	Increment cost per LY gained Increment cost per QALY
Results	LABA is less costly and more effective and therefore, dominates ICS+LABA

Study	Guillermo Ariza et al., 2012
Types of sensitivity analysis	Deterministic analysis (scenario) PREPOCOL patient cohort Probabilistic analysis (Monte Carlo simulation) Transition probability (Dirichlet distribution) Costs (gamma distribution) Utilities (beta distribution) Treatment effect (log normal distribution)
Sensitivity analysis results	Deterministic analysis (scenario) Results sensitive to PREPOCOL patient cohort Probabilistic analysis (Monte Carlo simulation) 65.7% and 94.5% of 1000 simulations indicate that LABA is less costly and more effective than ICS+LABA (salmeterol/fluticasone, formoterol/budesonide respectively)
Points to consider	Costs USD$ (2012), conversion 1 USD$ = 1771.13 COP Efficacy data for change in FEV_1 from a published network-meta-analysis (LABA versus ICS+LABA) and RCT (LABA versus LAMA) Efficacy data for exacerbations assumed Adverse events not included Utilities derived from the EQ-5D PSA considered Dirichlet (for transition probability), gamma (for costs), beta (for utilities), and log normal (for treatment effect) distributions, results presented in scatterplot Comparison of monotherapy (LABA) and dual therapies (ICS+LABA)

Study	Hertel et al., 2012
Sponsorship	MSD Ltd
Country	UK
Perspective	Health care system perspective
Study type	CEA/CUA
Comparators (relevant)	LABA (salmeterol) LAMA (tiotropium) LAMA+LABA (salmeterol + tiotropium) ICS+LABA (salmeterol/fluticasone) LAMA+ICS+LABA (tiotropium + salmeterol/fluticasone)
Population	Patients with severe COPD based on the GOLD criteria, associated with chronic bronchitis, with a history of frequent exacerbations and continue to have exacerbation despite existing bronchodilator therapy Assumed to start at age 64
Time horizon	Lifetime [30 years]
Type of model	Markov
Cycle length	1 month
Efficacy inputs	Exacerbations
Adverse events	Not included
Utilities	EQ-5D

Study	Hertel et al., 2012
Discounting	Costs and outcomes at 3.5%
Outcomes	Mean costs, LYs and QALYs Incremental cost per life years and QALYs gained for relevant comparisons not provided
Results	The ranking of treatments in terms of their estimated QALYs (from lowest to highest) was LABA, LAMA, ICS+LABA, LAMA+LABA then ICS+LABA + LAMA The treatments had the same ranking in terms of estimated lifetime costs
Types of sensitivity analysis	Deterministic analysis (one-way) Treatment effect Adverse events Costs Utilities Natural history of disease Discounting Patient characteristics Deterministic analysis (scenario) Assumptions of exacerbations Assumption of lung function benefit Assumptions of transition cycle Assumption of treatment switching Probabilistic analysis (Monte Carlo simulation) Parameter distributions not provided
Sensitivity analysis results	Results presented only for LAMA+ICS+LABA + roflumilast versus LAMA+ICS+LABA
Points to consider	Costs £(2008-11) Efficacy data from published mixed treatment comparison Results reported as mean costs and outcomes, incremental cost effectiveness ratios for relevant comparison not provided Adverse events not included Utilities derived from the EQ-5D Extensive sensitive analyses; however, results are not presented for relevant comparisons Distinct COPD severity population modelled Parameter distributions for PSA not provided Comparison of monotherapies (LAMA, LABA), dual therapies (ICS+LABA, LAMA+LABA) and triple therapy (LAMA+ICS+LABA)

Study	Briggs et al., 2010
Sponsorship	GlaxoSmithKline
Country	Multinational (USA, Eastern Europe, Western Europe, Asia/Pacific and other)
Perspective	Health care system perspective
Study type	CUA

Study	Briggs et al., 2010
Comparators	LABA (salmeterol) ICS (fluticasone propionate) ICS+LABA (salmeterol/fluticasone propionate) Placebo
Population	Patients aged 40-80 years, diagnosed with COPD with a FEV_1 < 60% of the predicted value and had smoking history of at least 10 pack-years
Time horizon	3 years
Type of model	Trial based analysis
Cycle length	N/A
Efficacy inputs	Mortality Quality of life
Adverse events	Not explicitly included
Utilities	EQ-5D
Discounting	Costs and outcomes at 3%
Outcomes	Incremental cost per QALY
Results	Report analysis (regional costs) ICUR for ICS+LABA versus placebo ranged from $21,500/QALY for Other to $77,100/QALY for USA ICUR for ICS+LABA versus LABA ranged from $13,000/QALY for Western Europe to $46,300/QALY for USA
Types of sensitivity analysis	Non-parametric bootstrap 1000 replications
Sensitivity analysis results	Non-parametric bootstrap At a willingness to pay of $50, 000/QALY, ICS+LABA is the most cost effective treatment in the Western European region
Points to consider	Costs USD$ (2007) Efficacy data from single RCT Adverse events not explicitly included Utilities derived from the EQ-5D Uncertainty assessed through non parametric bootstrap Comparison of monotherapy (LAMA, LABA), dual therapy (ICS+LABA), and placebo

Study	NCGC, 2010
Sponsorship	NICE
Country	UK
Perspective	Health care system perspective
Study type	CUA
Comparators	LAMA [Spiriva(tiotropium 18 µg)] ICS+LABA [Symbicort (budesonide 200 µg/ formoterol 6 µg, budesonide 400 µg/ formoterol 12 µg), Seretide (fluticasone 500 µg/salmeterol 50 µg)] Triple therapy (ICS+LABA + LAMA)
Population	Patients with severe to very severe COPD based on the GOLD criteria Assumed to start at age 66 and 46% female

Study	NCGC, 2010
Time horizon	4 years
Type of model	Markov
Cycle length	1 year
Efficacy inputs	Exacerbations Mortality (sensitivity analysis only) Quality of life (sensitivity analysis only)
Adverse events	Not included
Utilities	EQ-5D SGRQ (mapped to the EQ-5D)
Discounting	Costs and outcomes at 3.5%
Outcomes	Incremental cost per QALY
Results	Inspire, Uplift Data ICS+LABA is subject to extended dominance ICUR of triple therapy versus ICS+LABA is £187,697/QALY Inspire, Optimal Data ICS+LABA is subject to extended dominance ICUR of triple therapy versus ICS+LABA is £93,737/QALY Uplift, Optimal Data LAMA is subject to dominance ICUR of triple therapy versus ICS+LABA is £159,353/QALY
Types of sensitivity analysis	Deterministic analysis (one-way) Time horizon Costs of non-hospitalized exacerbations Exacerbation rate Deterministic analysis (scenario) Treatment affects exacerbation and stable quality of life effects Treatment affects exacerbation and mortality effects Deterministic analysis (scenario + one-way) Treatment affects exacerbation and stable quality of life effects + time horizon Treatment affects exacerbation and mortality effects + time horizon Probabilistic analysis (Monte Carlo simulation) Treatment effect (log normal) Utilities (normal, gamma, and beta distributions) Costs (gamma distribution)

Study	NCGC, 2010
Sensitivity analysis results	Deterministic analysis (one-way) Results insensitive to time horizon and costs of non-hospitalized exacerbations, but sensitive to exacerbation rate (contingent on the source of data). Deterministic analysis (scenario) Results sensitive to scenarios Deterministic analysis (scenario + one-way) Results insensitive to treatment affects exacerbation and stable quality of life effects scenario + time horizon Results sensitive to treatment affects exacerbation and mortality effects scenario + time horizon Probabilistic analysis (Monte Carlo simulation) Inspire + Uplift Data At a threshold of £20,000/QALY, LAMA has the highest probability of being cost effective Inspire +, Optimal Data At a threshold of £20,000/QALY, LAMA has the highest probability of being cost effective Uplift + Optimal Data At a threshold of £20,000/QALY, ICS+LABA has the highest probability of being cost effective
Points to consider	Costs in £ (2007/8) Efficacy data from three randomized controlled trials, using direct and indirect comparison In base case, treatment affects only exacerbation; in scenario deterministic analysis, treatment affects exacerbation and utilities as well as exacerbation and mortality Adverse events not included Utilities derived from the EQ-5D and SGRQ (mapped to the EQ-5D) A variety of sensitivity analyses; PSA considered log normal distribution for treatment effect; normal, gamma, and beta distributions for utilities; and gamma distribution for costs Comparison of monotherapy (LAMA), dual therapy (ICS+LABA) and triple therapy (LAMA+LABA+ICS); LABA alone was not considered

Study	Earnshaw et al., 2009
Sponsorship	GlaxoSmithKline
Country	US
Perspective	Third-party payer perspective
Study type	CEA/CUA
Comparators	ICS+LABA (fluticasone propionate 500 µg/salmeterol 50 µg) LABA (salmeterol 50 µg) ICS (fluticasone propionate 500 µg) no maintenance (placebo)
Populations	Patients with moderate to severe COPD based on the American Thoracic Society criteria, aged 40-80 with a baseline FEV_1 < 60% predicted, history of COPD, current or former smoker, poor reversibility of airflow obstruction

Study	Earnshaw et al., 2009
	Mean age 65 years
Time horizon	Lifetime
Type of model	Markov
Cycle length	1 year
Efficacy inputs	Exacerbations Mortality
Adverse events	Not Included
Utilities	EQ-5D SGRQ (mapped to the EQ-5D)
Discounting	Costs and outcomes at 3%
Outcomes	Increment cost per LY gained Increment cost per QALY
Results	ICERs for ICS+LABA versus placebo are $24,530/LY, $33,865/QALY, $11,405/exacerbation avoided, $23,456/hospital day avoided, $61/symptom –free day gained ICERs for ICS versus placebo $3,796/exacerbation avoided, $3,197/hospital day avoided Placebo dominates ICS in terms of incremental cost per life gained, QALY gained, and symptom-free day gained ICERs for LABA versus placebo are $15,098/LY, $20,797/QALY, $10,152/exacerbation avoided, $8,007/hospital day avoided, $38/symptom –free day gained
Types of sensitivity analysis	Deterministic analysis (one way) Transition probability Treatment effect Costs of prescription Costs of severe exacerbation Utilities Probabilistic analysis (Monte Carlo simulation) Gamma distribution (treatment effect, costs) Beta distribution (transition probability, utilities)
Sensitivity analysis results	Deterministic analysis (one way) Results sensitive to treatment effect Probabilistic analysis (Monte Carlo simulation) At a threshold of $50,000/QALY, the probability of ICS+LABA being more cost effective than no therapy is 78%
Points to consider	Costs USD$ (2006) Efficacy data from a published RCT Adverse events not included Utility weights derived from published studies which used the EQ-5D and mapped SGRQ to the EQ-5D Results reported only as incremental cost effectiveness ratios compared to placebo Extensive sensitivity analyses; PSA considered beta (for transition probability, utilities) and gamma (for treatment effect, costs) distributions

Study	Earnshaw et al., 2009
	Comparison of monotherapies (LAMA, ICS), dual therapy (ICS+LABA) and no maintenance

Study	Oba, 2009
Sponsorship	None disclosed
Country	US
Perspective	Third-party payer perspective
Study type	CUA
Comparators	ICS+LABA (fluticasone propionate 500 µg/salmeterol 50 µg) LABA (salmeterol 50 µg) ICS (fluticasone propionate 500 µg) Placebo
Population	Patients with moderate to very severe COPD based on the GOLD criteria Mean age 65, 76% male, 43% current smoker
Time horizon	3 years
Type of model	Markov
Cycle length	3 months
Efficacy inputs	Exacerbation Mortality
Adverse events	Not included
Utilities	SGRQ (mapped to the EQ-5D)
Discounting	Costs and outcomes at 3%
Outcomes	Incremental cost per QALY
Results	ICUR for ICS+LABA versus placebo is $52,046/QALY LABA and ICS are subject to extended dominance by ICS+LABA compared to placebo
Types of sensitivity analysis	Deterministic analysis (one-way) Transition probability Treatment effect Costs Discounting Probabilistic analysis (Monte Carlo simulation) Transition probabilities (beta distribution) Treatment effect (beta distribution) Utilities (beta distribution) Costs (gamma distribution) Probabilistic analysis (Monte Carlo simulation using pooled data) Transition probabilities (beta distribution) Treatment effect (beta distribution) Utilities (beta distribution) Costs (gamma distribution)

Study	Oba, 2009
Sensitivity analysis results	Deterministic analysis (one-way) Results are sensitive to costs, all-cause mortality, hospitalization, and utility weights Probabilistic analysis (Monte Carlo simulation) At a willingness to pay of under $52,800/QALY, placebo is the most cost effective treatment At a willingness to pay of $52,800/QALY or greater, ICS+LABA is the most cost effective treatment Probabilistic analysis (Monte Carlo simulation using pooled data) At a willingness to pay of under $55,200/QALY, placebo is the most cost effective treatment At a willingness to pay of $55,200/QALY to$ 62,400/QALY, LABA is the most cost effective treatment At a willingness to pay greater than $62,400/QALY, ICS+LABA is the most cost effective treatment
Points to consider	Costs USD$ (2006) Efficacy data from a RTC: sensitivity analysis using published systematic review Adverse events not included Utility weights mapped SGRQ to the EQ-5D PSA considered beta (for transition probability), gamma (for costs), beta (for utilities), results are presented in cost-effectiveness acceptability curve Comparison of monotherapies (LABA, ICS), dual therapy (ICS+LABA) and no treatment

Study	Dal Negro et al., 2007
Sponsorship	GlaxoSmithKline
Country	Italy
Perspective	Societal perspective
Study type	CEA
Comparators	Placebo ICS+LABA (salmeterol 50 µg/fluticasone 500 µg, formoterol 160 µg/budesonide 4.5 µg) ICS (fluticasone 500 µg) LABA (salmeterol 50 µg)
Population	Whole Italian population of COPD patients (mild to very severe COPD based on the GOLD criteria), aged 20 years and over
Time horizon	Lifetime
Type of model	Markov
Cycle length	1 year
Efficacy inputs	Exacerbation Symptom-free days
Adverse events	Not Included
Utilities	N/A
Discounting	None

Study	Dal Negro et al., 2007
Outcomes	Incremental cost per exacerbation per patient Incremental cost per symptom-free days per patient
Results	All strategies dominate control with the exception of ICS which is more costly ICER for ICS+LABA (salmeterol/fluticasone) versus LABA (salmeterol) is €679.55/exacerbation and €3.31/symptom-free day ICER for ICS+LABA (formoterol/budesonide) versus LABA (salmeterol) is €1,392.38/exacerbation and €3.48/symptom-free day
Types of sensitivity analysis	Deterministic analysis (one-way) Treatment effect Costs Deterministic analysis (threshold) Treatment effect Costs
Sensitivity analysis results	Deterministic analysis (one-way) Results sensitive to treatment effect and costs Deterministic analysis (threshold) If the average initial population of exacerbations/patient year was 0.59, relative risk of exacerbations was 0.734, cost of hospitalization was €1,584, and treatment pharmaceutical cost was € 91.28, then the differential costs between ICS+LABA and control would be zero
Points to consider	Costs € (2003/5) Efficacy data from two RCT Adverse events not included Utilities were not considered Only intermediate outcomes were considered PSA was not conducted Comparison of monotherapies (LABA, ICS) and dual therapies (ICS+LABA) and placebo

Study	Gagnon et al., 2005
Sponsorship	GlaxoSmithKline
Country	US
Perspective	Third-party payer perspective
Study type	CEA
Comparators	ICS+LABA* LABA ICS Comparison (no exposure to ICS or LABA, at least 90 days exposure to other COPD drugs)
Population	Patients aged 40 or over with at least two outpatient encounters or at least hospital admission (coded as chronic bronchitis, emphysema, or COPD) and no evidence of cystic fibrosis, bronchiectasis or lung cancer Mean age of 66 years

Study	Gagnon et al., 2005
Time horizon	3 years Lifetime
Type of model	Observational cohort analysis
Cycle length	N/A
Efficacy inputs	All-cause mortality
Adverse events	Not included
Utilities	N/A
Discounting	Costs and outcomes at 5%
Outcomes	Incremental cost per LY gained
Results	3 year time horizon LABA dominated ICS and comparison (no LABA or ICS) ICER for ICS+LABA versus LABA is $91,430/LY Lifetime horizon LABA dominated ICS ICER for LABA versus comparison (no LABA or ICS) is $6,110/LY ICER for ICS+LABA versus LABA is $27,570/LY
Types of sensitivity analysis	Non-parametric bootstrap method 1000 bootstraps
Sensitivity analysis results	Non-parametric bootstrap method Three year time horizon Results from the non-parametric bootstrap method suggest that LABA may dominate both ICS and comparison (no LABA or ICS) At a willingness to pay under $91,000/LY, LABA is the most cost effective treatment At a willingness to pay of $91,000/LY and greater, ICS+LABA is the most cost effective treatment Lifetime horizon Results from the non-parametric bootstrap method suggest that LABA may dominate ICS At a willingness to pay under $6,100/LY, comparison (no LABA or ICS) is the most cost effective treatment At a willingness to pay of $6,100/LY to $27,500/LY, LABA is the most cost effective treatment At a willingness to pay greater than $27,500/LY, ICS+LABA is the most cost effective treatment
Points to consider	Costs USD$ (2001) Efficacy data from a published observational cohort study of treatment effectiveness Adverse events not included Utility value not considered Reference treatment in analysis is LABA for 3 year time horizon and no treatment for lifetime horizon Results reported as incremental cost effectiveness ratios comparing placebo to alternative treatments which are not presented in a meaningful way Gompertz distribution considered in parametric proportional hazards regression

Study	Gagnon et al., 2005
	model Non-parametric bootstrap method considered Comparison of monotherapies (LAMA, ICS), dual therapy (ICS+LABA) and comparison (not LABA or ICS, but other COPD therapy)

* Unclear if combination or single inhalers of ICS and LABA

Appendix B – De novo Economic Evaluation

Research Question

RQ2. Based on a de novo economic model, what is the cost-effectiveness of ICS in combination with LABA for chronic treatment of COPD compared to single and combination therapies incorporating LABA, LAMA and ICS?

Study Objectives

Based on the research question the objectives of the study were to address the following specific questions:

- What is the cost effectiveness of ICS+LABA combination versus ICS and LABA as dual therapy or within triple therapy?
- What is the cost effectiveness of ICS+LABA combination therapy compared to ICS or LABA?
- What is the cost effectiveness of ICS+LABA combination therapy combined with LAMA versus LAMA alone or LAMA+LABA given as dual therapy (two separate inhalers) or LAMA +ICS?

De novo Economic Evaluation

Model Structure

The long term costs and quality adjusted life years (QALYs) of ICS plus LABA combination therapies compared to single or combination therapies incorporating LABA, LAMA and ICS in the treatment of COPD was assessed using a Markov model. These estimates can then be used to estimate the relative cost effectiveness of alternative reimbursement strategies for the coverage of ICS plus LABA combination therapies.

In modelling the disease progression in COPD, previous models have assessed disease severity by categorising patients by their FEV_1% which decreases with time leading to transitions from milder to more severe states. Both rates of exacerbations and mortality have been shown to increase with disease severity and the proportion of exacerbations requiring hospitalizations similarly increases with severity. Thus, similar to previous models, the model is comprised of five mutually exclusive states representing COPD disease severity and death. Death is an absorbing state meaning that when individuals enter this state, they remain within the state. The three states of COPD severity are defined according to GOLD guideline criteria for COPD diagnosis which classifies disease severity based on post bronchodilator FEV_1.[1] Moderate encompasses those patients with an FEV_1 50% and 79% of normal, severe between 30% and 49% of normal and very severe between below 30% of normal (Figure 1 Schematic of Markov Model).

The cycle length of the model is one month with a lifetime horizon (maximum of 30 years). The model is adaptable, allowing for the estimation of the costs and QALYs associated with COPD treatments in a cohort of patients at any age from 40 to 100 years and with any severity of COPD.

During each cycle of the model, patients in each of the disease model states may experience an exacerbation of their COPD, progression of their disease or die either due to COPD or due to other causes. Within the mild, moderate and severe states patients who experience an exacerbation may either progress to the next more severe state, die due to a hospital treated exacerbation, die due to background mortality or remain within the same COPD severity state. Patients who do not experience an exacerbation may progress to the next more severe state, die due to background mortality or remain within the same COPD severity state. Patients within the very severe state may experience the same outcomes, except they do not progress to a more severe COPD state.

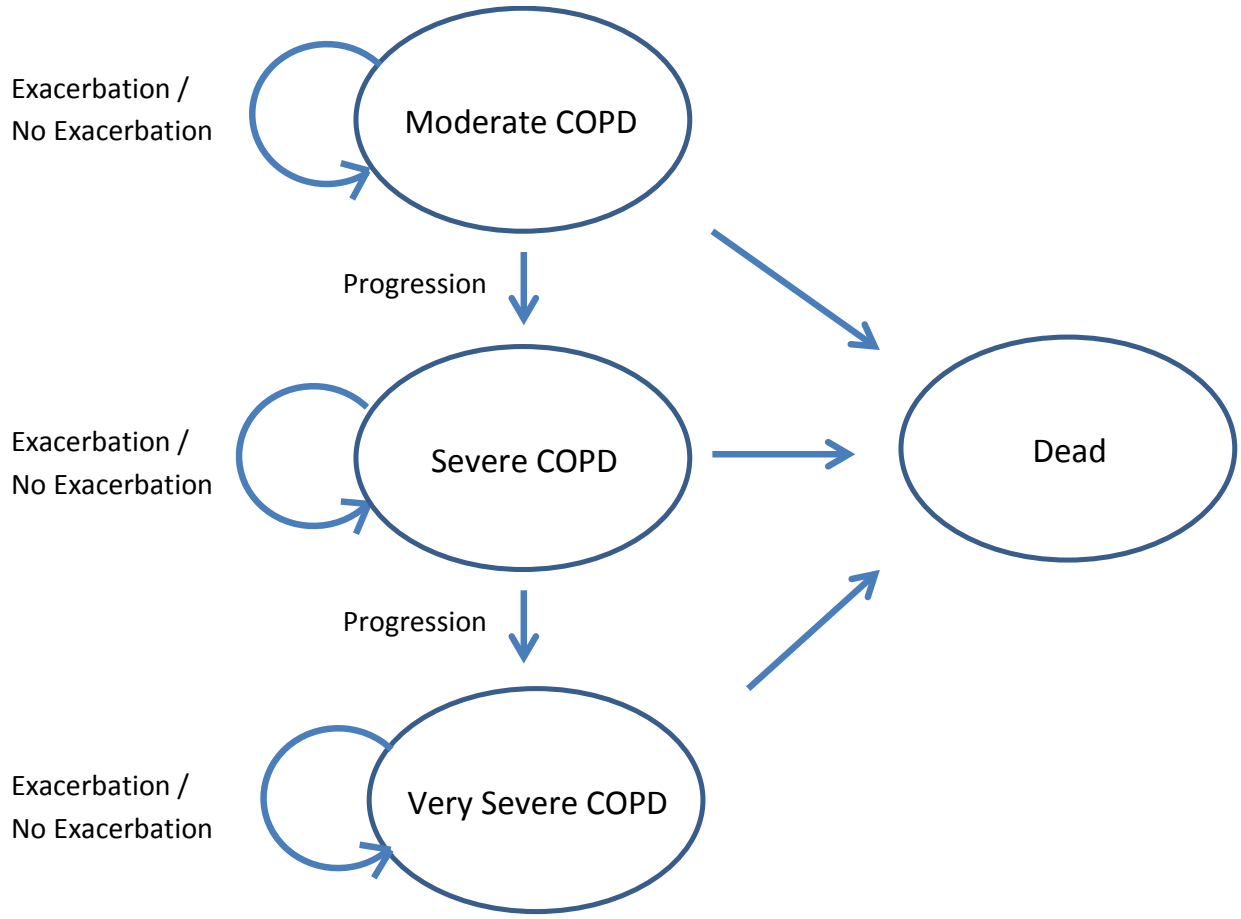


Figure 1 Schematic of Markov Model

Data Inputs

Data Values

Data used within the economic model are provided in Appendix B1 – Data Estimates. Details of data sources are provided below.

Progression of Disease

The progression of COPD depends on the baseline FEV_1 of the cohort entering the model the rate of decline in FEV_1 over time. The annual rate of decline in lung function in patients with COPD has been estimated to be 52 mL. [125]

Patients were assumed to enter the model with a baseline post bronchodilator FEV_1 equal to the midpoint of each of the COPD category severities, 65% of normal FEV_1 in moderate, 40% of normal FEV_1 in severe. The predicted normal FEV_1 for the patient population modelled was estimated using predictive equations from a study which provides estimates for a general population of non-smoking men and women: in males FEV_1 (mean) = (0.0414 X height) – (0.0244 X age) – 2.190, in females FEV_1 (mean) = (0.0342 X height) – (0.0255 X age) – 1.578 (height in cm). [126] The cohort's baseline lung function is then estimated as the product of the baseline FEV_1 percentage, based on COPD severity, and the predicted normal FEV_1.

The time to progression from moderate to severe and severe to very severe disease can then be derived based on the baseline FEV_1 of the cohort with each disease severity and the rate of lung function decline.

Exacerbations

Exacerbations within the model are classified as either moderate, requiring community based care, or severe, requiring hospital based care. The rate of total exacerbations was estimated based on the placebo arm of the TORCH study which compared the efficacy of salmeterol alone, fluticasone alone, and salmeterol plus fluticasone versus placebo. [127] Patients within the placebo arm were not receiving either inhaled long acting beta agonists or inhaled or oral corticosteroids and are therefore suitable for providing an estimate of the exacerbation rate in untreated patients. The annual exacerbation frequency per GOLD stage was estimated and was converted within the model to a monthly transition probability.

The proportion of total exacerbations requiring hospitalization was derived from a pooled analysis of the placebo arms of the indacaterol trials. [128] Estimates by COPD severity were possible as the patient's most recent pre-bronchodilator FEV_1 value was recorded before the exacerbation and was used to classify the severity of disease.

Mortality

Patients with COPD are at an increased risk of mortality relative to the general population. In particular, hospital exacerbations of COPD are associated with increased mortality in patients with COPD. As treatments for COPD have been shown to reduce exacerbations, to model the effect of these reductions on mortality it is important to model the background risk of mortality and the hospital exacerbation associated mortality separately within the model. To do so, the hospital associated mortality must be removed from the background mortality otherwise double counting of mortality will occur.

This was conducted by first applying relative increase in all-cause mortality in patients with varying severities of disease to the age specific mortality rates derived from Canadian Life Tables to calculate the all-cause mortality in COPD patients by COPD severity, age and gender. [129,130]

The age specific hospital COPD exacerbation mortality risk was obtained from the 2008 UK National COPD Audit Report. [131] Based on data from 9,716 patients, the age specific hospital mortality due to

COPD exacerbation was estimated. To estimate the mortality rate due to hospital exacerbations of COPD by age and COPD severity, these risks were applied to the risk of severe exacerbation by severity of COPD derived from Price 2011 (see Exacerbations). [128]

Utilities

Utilities by disease severity

The literature was reviewed both with respect to utility values associated with the COPD health states as defined within the GOLD guidelines and with respect to the utility decrement associated with both community treated and hospitalized exacerbations.

There were six studies reporting utility values by COPD severity;[132-137] although, only four studies provided estimates of utility values associated with all three categories of COPD severity included within the model. [134-136] Stahl and Borg both used the EQ5D to elicit quality of life assessments from Swedish COPD patients and yielded similar estimates of utility values by COPD severity; however, the results in moderate and severe patients within the Stahl study were somewhat counterintuitive, producing a slightly higher utility in severe than in moderate patients.

In the base cases analysis, the utility values derived by Borg et al as part of a Swedish cost of illness study were used. In the study, quality of life was assessed through completion of the EQ5D by 212 individuals with COPD. The EQ5D was scored using the UK index tariff to allow estimation of the mean utility value for each of the GOLD COPD severity states with estimates of uncertainty. A number of subsequent cost effectiveness analyses have used the utility values from this study.[138,139]

Values from two studies conducted by Rutten-van Molken were used within sensitivity analyses.[134] One study estimated utility values for COPD health states using both a visual analogue scale and time trade off method.[134] The survey was conducted from a societal perspective with 239 Dutch adults drawn from the general public. Values were similar in severe and very severe states to those reported in Borg and Stahl, but higher than other reported values within the mild and moderate states. The second study derived utility values from the UPLIFT trial, a randomized controlled trial of tiotropium versus placebo, however these values apply only to moderate, severe and very severe COPD health states but were more consistent with the estimates of Borg. [133]

A study by Spencer provided estimates of the utilities based on the British Thoracic Society classification of disease severity as derived from the Health Survey for England which does not match the GOLD classification used within the model. [132]The final study derived values from a clinical trial of roflumilast; however, only values for severe and very severe were reported and therefore they would not be applicable within the current model.[137]

Utilities for COPD exacerbations

Sourcing the utility deficit associated with COPD exacerbations is challenging. A large number of studies estimated a percentage utility deficit with exacerbations based on expert clinical opinion due to the lack of evidence in this area.[132,135,139,140] There are, however, some studies which have measured the utility

deficit with COPD exacerbations. After assessing the literature, two studies by Goossens and O'Reilly were chosen as the sources of the utility values for COPD exacerbations within this analysis.[141,142] Details of all of the studies are provided below, for comparison purposes as are the reasons for the selection of the two studies and the exclusion of the remaining analyses from the model.

Rutten van Molken used the time trade off method to estimate the utility deficit associated with a single mild exacerbation within a year timeframe and a single severe exacerbation within a one year time frame from a Dutch societal perspective. Many studies have allocated this utility deficit over the time course of a single cycle of a model in order to estimate the utility deficit of an exacerbation.[137] This results in an annual utility deficit of 0.01 QALYs for community treated exacerbations and 0.042 for hospital treated exacerbations. These would equate to a one month utility deficits of 0.504 for hospital exacerbations and 0.12 for community exacerbations. These values were not used within the model, as direct measures of disutility in COPD exacerbations were considered more robust.

In a study by Menn, the quality of life in patients with COPD exacerbations was measured using the EQ5D, SF12 and SGRQ in German hospitalized patients. [143] Mean utility values as measured using the EQ5D ranged from 0.60 (stage IV) to 0.62 (stage III) at admission and from 0.75 (stage IV) to 0.84 (stage III) at discharge. This study did not provide information suitable for the current model as it included only patients with GOLD III and IV.

Paterson also used the EQ5D to assess the quality of life of patients experiencing an acute exacerbation of chronic bronchitis in a Scottish general practice.[144] Patients completed the EQ5D at the presenting visit and one week after completion of treatment. The mean change in utility value from baseline to follow up was 0.17 (SD 0.24). Only 53% of patients were considered clinically cured at the follow up assessment and no further assessment was made. The lack of detail within the published report regarding baseline and follow up values precludes the use of this reference within the model.

The two studies which were used to source the utility data for exacerbations within the current model both directly measured the quality of life of patients experiencing an exacerbation. The first, a study by O'Reilly administered the EQ5D to COPD patients hospitalized for an exacerbation both at the time of admission and the time of discharge. [141] The second by Goossens measured the utility deficit of patients experiencing an exacerbation requiring a clinic visit at four time-points. [142] As these represent the most direct measures of disutility associated with exacerbations, they were used within the model.

For hospital based exacerbations, a similar approach was taken as in an economic model by Hoogendorn based on the values from the O'Reilly study. [141,145]The average utility value on admission to hospital as measured by O'Reilly in UK patients was -0.077, rising to 0.576 at discharge, after a mean of 11 days in hospital. Based on the assumptions that a patient's utility returns to normal by 4.5 months [138] and that there is a linear increase between hospital admission and discharge and between discharge and 4.5 months the disutility associated with a hospitalized exacerbation was estimated. This disutility was then allocated to the month in which the exacerbation occurred. The estimated one month loss in utility within the model for a hospitalized exacerbation is 0.3933.

In the study by Goossens, the EQ5D was administered to 59 patients experiencing a community based exacerbation of COPD as defined by a worsening of symptoms lasting 3 or more days and requiring a change in treatment. Quality of life was assessed at baseline, day 7, day 14 and at day 42. Participants lost an average of 0.00896 QALYs (SD 0.0086) during the exacerbation. This disutility was allocated to the month in which the community acquired exacerbation occurred. The one month loss in utility within the model for a community exacerbation is 0.1075.

Resource Use and Costs

The costs of COPD can be subdivided into the costs associated with maintenance treatment, those associated with exacerbations, both community based and hospital based and the costs associated with drug therapies. All costs were inflated to 2013 dollars using the Bank of Canada Inflation calculator.[146]

COPD Maintenance Costs

Maintenance costs are those associated with the day to day management of COPD during the time when patients are not experiencing an exacerbation. These include drug acquisition, oxygen therapy, laboratory and diagnostic tests and clinic visits. Canadian specific maintenance costs for the treatment of COPD by disease severity were estimated by Spencer et al.[132] The costs were reported for patients with mild to moderate COPD, severe COPD and very severe COPD.

Costs of Exacerbations

The cost of treating a community based exacerbation in Canada was estimated at $722.02 and the cost of a hospital based exacerbation was estimated at $10,765.00.[147] These estimates were based on resource use data sourced from the Canadian study entitled, Resource Utilization Study in COPD (RUSIC), which collected data on the health care resources associated with moderate and severe exacerbations in COPD over a 52 week period for 609 patients. Information was collected with respect to emergency room visits, outpatient visits and hospitalizations and included physician visits, laboratory and diagnostic testing, medications, length of stay and mode of transportation. The costs included within the model estimate were limited to those reimbursed through the healthcare system. Costs were obtained from Ontario provincial sources, hospital databases and published literature.

Costs of Medications

Costs for medications were based on the most commonly prescribed dose for each product within the OPDP. Daily required dosages were based on clinical guidelines. Annual costs were derived from the Ontario Drug Formulary and also included an 8% pharmacy mark-up and four $8.83 dispensing fees annually. LAMA+LABA as a therapy is modelled as dual therapy (two separate inhalers) rather than combination therapies which will be the focus of a further class review,

External Validation

The mortality rate forecasted by the model was validated externally against three year survival data derived from the Copenhagen City Heart Study and the Copenhagen General Population Study. [148]

Treatment Effectiveness

The nature of the progression of COPD makes the modelling of treatment effects prone to double counting. Incorporating the effect of treatment on FEV_1%, will lead to a delay in transitions across disease severity and thus, an indirect effect on both exacerbation rates and mortality. Incorporating the effect of treatment on exacerbations will have an indirect effect on mortality due to reduced hospitalized exacerbations; assuming mortality due to exacerbations is incorporated. Thus, analyses which incorporate any two of the effect of treatment on FEV_1%, exacerbations and mortality will involve double counting of treatment effects and bias in the estimates of cost effectiveness. For this analysis, effectiveness was modelled in terms of the effects on exacerbation rates which will have an indirect effect on mortality.

Data from the companion systematic review on the relative risk of exacerbation across all disease severities were used within this analysis.

Treatment Adverse Effects

Inhaled corticosteroids have been associated with an increased incidence of pneumonia in COPD patients and therefore the comparative effects of treatments on rates of pneumonia was incorporated within the model using data from the network meta-analysis. The utility decrements associated with both community treated and hospitalized pneumonia were sourced from a previously published economic analysis which reported a loss of 0.006 QALYs and 0.008 QALYs respectively.[149] The costs of treatment were derived from Canadian sources. Based on an analysis of Alberta administrative databases the 2013 cost of treating a hospital case of pneumonia was estimated at $6,148 and the cost of treating a community based case was $183 including physician and medication costs.[150] The same analysis found that 23.7% of pneumonia cases required hospitalization with a 12.93% mortality rate for hospitalized cases. The excess mortality due to hospitalized pneumonia in those receiving COPD treatments was incorporated within the model.

Cost Effectiveness

For comparisons where clinical data were available, a cost utility analysis was conducted. For comparisons where no clinical data were available, only a simple comparison of monthly drug costs can be made.

For the cost utility analyses, lifetime costs and effects as measured by life years and quality adjusted life years gained associated with COPD treatments are estimated via the model. To obtain estimates of costs and QALYs for each drug class, results for individual treatments were weighted by the proportion of use for each product within each class of disease severity.

Costs and QALYs are both discounted at a standard rate of 5% per annum.[5] The cost effectiveness of each of the treatments is then estimated as the cost per quality adjusted life year gained relative to the comparator treatment.

For the base analysis, results were presented for each drug class for the three degrees of disease severity for male COPD patients aged 70 years. Subgroup analysis was conducted by varying the patient age (60, 70 and 80) and gender (male and female).

For the first question, the ICS+LABA drug class is compared to ICS and LABA drug classes given concurrently as dual therapy.

For the second question, the ICS+LABA drug class is compared to ICS and to LABA as monotherapies.

For the third question, ICS+LABA combination products combined with LAMA is compared to LAMA alone and LAMA in combination LABA and in combination with ICS.

Deterministic Sensitivity Analyses

A deterministic sensitivity analysis was conducted to determine impact of the following parameter inputs on the results: utility values, time horizon (1, 5, 10 years), discounting (0% and 3%), and assumptions relating to the impact of treatments on the rate of pneumonia.

Probabilistic Sensitivity Analyses

A probabilistic sensitivity analysis was conducted in order to estimate the impact of parameter uncertainty on the cost effectiveness. The parameters included within the PSA and their corresponding distributions are reported in Appendix B1. A gamma distribution was used for costs and the probability of an exacerbation. A beta distribution was used for the probability that an exacerbation resulted in hospitalization and for utilities by COPD severity. A log normal distribution was used for the relative risks associated with treatment effect. Finally, a normal distribution was used for the disutilities associated with community and hospital exacerbations. To model the impact of hospital exacerbations on utility, a Cholesky decomposition matrix was employed to account for the correlation between the admission and discharge utility value for hospital exacerbations.

The results of the PSA are presented through 95% CI around outcomes and by a cost effectiveness acceptability curve depicting the probability that ICS+LABA combination products are cost effective when compared to each drug given different threshold values for a QALY.

Findings

Base Case

The base case sought to answer the three specific objectives of the economic analysis the results of which are presented below. The base case analysis is focused on males, 70 years of age beginning treatment with at least moderate COPD, at least severe COPD and with very severe COPD. Analysis for additional subgroups including females and different ages is presented within the subsequent section entitled Analysis by Patient Sub Populations.

With respect to the comparative cost effectiveness of ICS+LABA combination versus ICS and LABA as dual therapy the lack of clinical data precluded the inclusion of this comparison within the network

meta-analysis. Therefore, based on the assumption that there is no difference in efficacy or adverse events between administration of an ICS and LABA via a single inhaler and administration via two separate inhalers, a cost minimization analysis was conducted.

In the case of both the budesonide/formoterol combination and the fluticasone/salmeterol combination, the cost of the single inhaler combination product is lower than the cost of receiving the two medications via separate inhalers. Receiving both budesonide and formoterol via separate inhalers has an estimated monthly cost of $96.90 and for both fluticasone and salmeterol via separate inhalers the monthly cost is substantially higher at $157.70. The costs are lower and more comparable between the products when a combination product is used with the monthly cost of the budesonide/formoterol combination being $93.72 compared with $109.63 with fluticasone/salmeterol.

The second objective was to compare the cost effectiveness of ICS+LABA combination therapy with ICS alone and LABA alone. In all severities of COPD, ICS+LABA combination therapy was both more costly and more effective than LABA alone. The incremental cost effectiveness ratio for the ICS+LABA combination versus LABA in patients with at least moderate COPD was $261,539/QALY, in patients with at least severe COPD it was $98,911/QALY and in those with very severe COPD it was $79,448/QALY (Table 1). Based on a willingness to pay threshold of $50,000/QALY, the ICS+LABA combination would not be considered cost effective as compared with LABA alone in any of these patient populations. With respect to the comparison of the ICS+LABA combination with ICS alone, the combination dominated ICS alone, being both less costly and more effective than ICS alone. The lack of cost effectiveness of ICS alone in COPD, however, does not support the use of this treatment strategy in COPD.

Table 1 Base Case - ICUR ICS+LABA versus LABA; ICS

	INCREMENTAL COST PER QALY GAINED ICS+LABA VERSUS:	
	LABA	ICS
At least Moderate COPD	$261,539	ICS+LABA dominates ICS
At least Severe COPD	$98,911	ICS+LABA dominates ICS
At least Very Severe COPD	$79,448	ICS+LABA dominates ICS

The third question was with respect to the cost effectiveness of triple therapy with an ICS+LABA combination product combined with a LAMA as compared with LAMA alone, LAMA+LABA or LAMA+ICS. There was no clinical data on which to base a comparison with LAMA+ICS and therefore this comparison was omitted. In comparison with LAMA alone, triple therapy is both more costly and more effective resulting in an incremental cost effectiveness ratio ranging from approximately $85,000/QALY to $160,000/QALY (Table 2). At a willingness to pay threshold of $50,000/QALY, triple therapy with ICS+LABA combination with LAMA would not be considered cost effective compared with LAMA alone.

As compared with LAMA+LABA, triple therapy with an ICS+LABA combination with a LAMA resulted in a cost effectiveness ratio of $28,767 per QALY in patients with at least moderate COPD and triple therapy was the dominant therapy, meaning it was both more effective and less costly, in patients with at least severe or very severe COPD (Table 2). Interpretation of these results should be put into context with the

comparative cost effectiveness of the combination of LAMA+LABA versus LAMA alone. In most cases, LAMA alone dominated the use of LAMA+LABA as it was both more effective and less costly. The rationale of moving from single therapy with LAMA to dual therapy with LAMA+LABA, based on cost effectiveness considerations, is not supported by the analysis and this should be taken into consideration when assessing the cost effectiveness of triple therapy.

Table 2 Base Case - ICUR ICS+LABA with LAMA versus LAMA; LAMA+LABA

	INCREMENTAL COST PER QALY GAINED ICS+LABA with LAMA VERSUS:	
	LAMA	LAMA+LABA
At least Moderate COPD	$160,957	$28,767
At least Severe COPD	$85,945	ICS+LABA with LAMA dominates LAMA+LABA
Very Severe COPD	$85,522	ICS+LABA with LAMA dominates LAMA+LABA

Analysis by Patient Sub Populations

Analysis was conducted for cohorts of males starting age 60 and age 80 for each severity of COPD and for females starting age 60, 70 and 80 for each severity of COPD. The results are presented in Table 3 and Table 4.

With respect to both the comparative cost effectiveness of ICS+LABA combination therapy versus ICS alone and LABA alone and the comparison of ICS+LABA combination therapy in addition to LAMA versus LAMA alone and versus LAMA+LABA, the results within each of the subgroups were consistent with those seen in the base case analysis.

Table 3 Analysis by Sub Populations - ICUR ICS+LABA versus LABA; ICS

		INCREMENTAL COST PER QALY GAINED ICS+LABA VERSUS:	
		LABA	ICS
Males 60 years	**At least Moderate COPD**	$308,410	ICS+LABA dominates ICS
	At least Severe COPD	$97,570	ICS+LABA dominates ICS
	Very Severe COPD	$81,801	ICS+LABA dominates ICS
Males 80 years	**At least Moderate COPD**	$205,355	ICS+LABA dominates ICS
	At least Severe COPD	$95,167	ICS+LABA dominates ICS
	Very Severe COPD	$76,074	ICS+LABA dominates ICS
Females 60 years	**At least Moderate COPD**	$167,809	ICS+LABA dominates ICS
	At least Severe COPD	$77,146	ICS+LABA dominates ICS
	Very Severe COPD	$75,063	ICS+LABA dominates ICS
Females 70 years	**At least Moderate COPD**	$164,749	ICS+LABA dominates ICS
	At least Severe COPD	$78,009	ICS+LABA dominates ICS
	Very Severe COPD	$71,626	ICS+LABA dominates ICS
Females 80 years	**At least Moderate COPD**	$154,745	ICS+LABA dominates ICS
	At least Severe COPD	$77,942	ICS+LABA dominates ICS
	Very Severe COPD	$67,788	ICS+LABA dominates ICS

Table 4 Analysis by Sub Populations - ICUR ICS+LABA with LAMA versus LAMA; LAMA+LABA

		INCREMENTAL COST PER QALY GAINED ICS+LABA with LAMA VERSUS:	
		LAMA	LAMA+LABA
Males 60 years	**At least Moderate COPD**	$145,813	$21,837
	At least Severe COPD	$76,430	ICS+LABA with LAMA dominates LAMA+LABA
	Very Severe COPD	$79,080	ICS+LABA with LAMA dominates LAMA+LABA
Males 80 years	**At least Moderate COPD**	$164,500	$34,344
	At least Severe COPD	$91,665	$3,397
	Very Severe COPD	$89,444	ICS+LABA with LAMA dominates LAMA+LABA
Females 60 years	**At least Moderate COPD**	$107,160	$10,016
	At least Severe COPD	$62,812	ICS+LABA with LAMA dominates LAMA+LABA
	Very Severe COPD	$70,852	ICS+LABA with LAMA dominates LAMA+LABA
Females 70 years	**At least Moderate COPD**	$121,691	$15,391
	At least Severe COPD	$69,748	ICS+LABA with LAMA dominates LAMA+LABA
	Very Severe COPD	$75,342	ICS+LABA with LAMA dominates LAMA+LABA
Females 80 years	**At least Moderate COPD**	$133,736	$22,597
	At least Severe COPD	$76,236	ICS+LABA with LAMA dominates LAMA+LABA
	Very Severe COPD	$78,392	ICS+LABA with LAMA dominates LAMA+LABA

Deterministic Sensitivity Analysis

One-way sensitivity analyses found the results to be robust to the incorporation of alternative utility values, to changes in time horizon including 1 year, 5 year and 10 years, discount rates of 0% and 3% and the assumption that treatment has no impact on the rate of pneumonia.

Probabilistic Sensitivity Analysis

The results of the Monte Carlo Simulation as they pertain to each of the objectives of the analysis are presented below.

With respect to the comparative cost effectiveness of ICS+LABA combination therapy with LABA alone, the combination product was more effective in 73% of replications, but more costly in 99.8% of replications (Figure 2). As illustrated within the cost effectiveness acceptability curve, at a willingness to pay of $50,000 per QALY there is only a 6% chance that the ICS+LABA combination product is more cost effective than LABA alone (Figure 3).

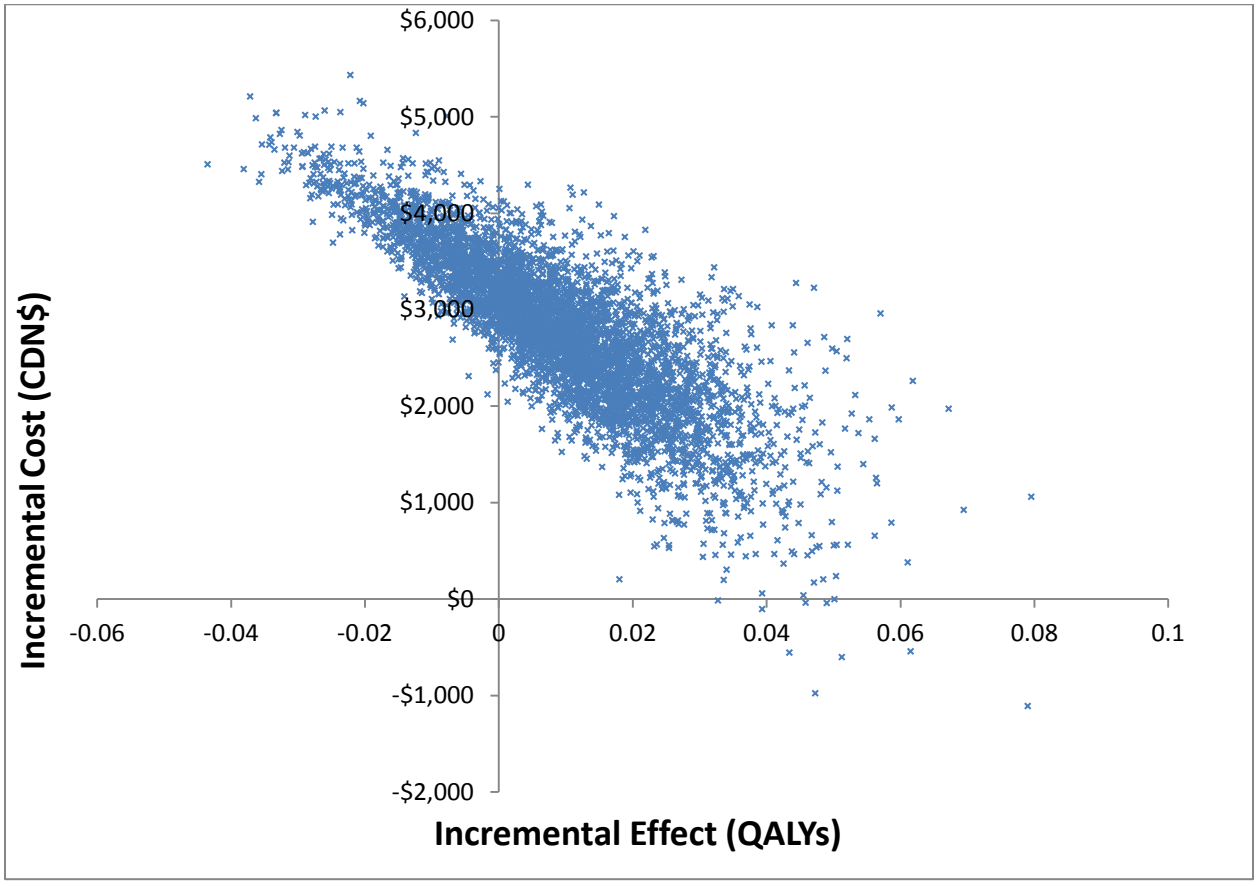


Figure 2 Incremental Cost Effectiveness Plane for ICS+LABA versus LABA

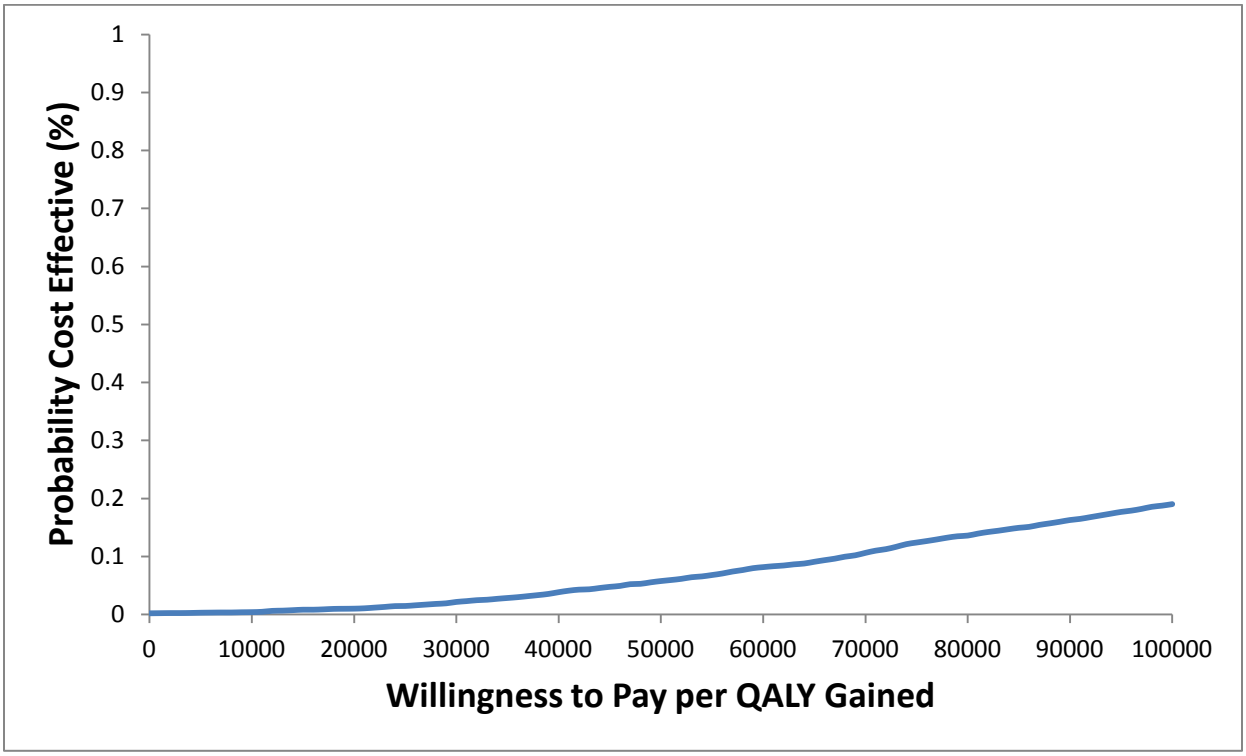


Figure 3 Cost Effectiveness Acceptability Curve for ICS+LABA versus LABA

With respect to the comparative cost effectiveness of ICS+LABA versus ICS alone, the combination product was more effective in 98% of simulations and less costly in 71% of simulations leading to the combination being dominant over ICS alone in 71% of simulations (Figure 4). At a willingness-to-pay of $50,000 per QALY, there is a 92% probability that the combination product is the most cost effective therapy (Figure 5). This result, however, should be considered in context given the lack of cost effectiveness of ICS as a treatment option in COPD.

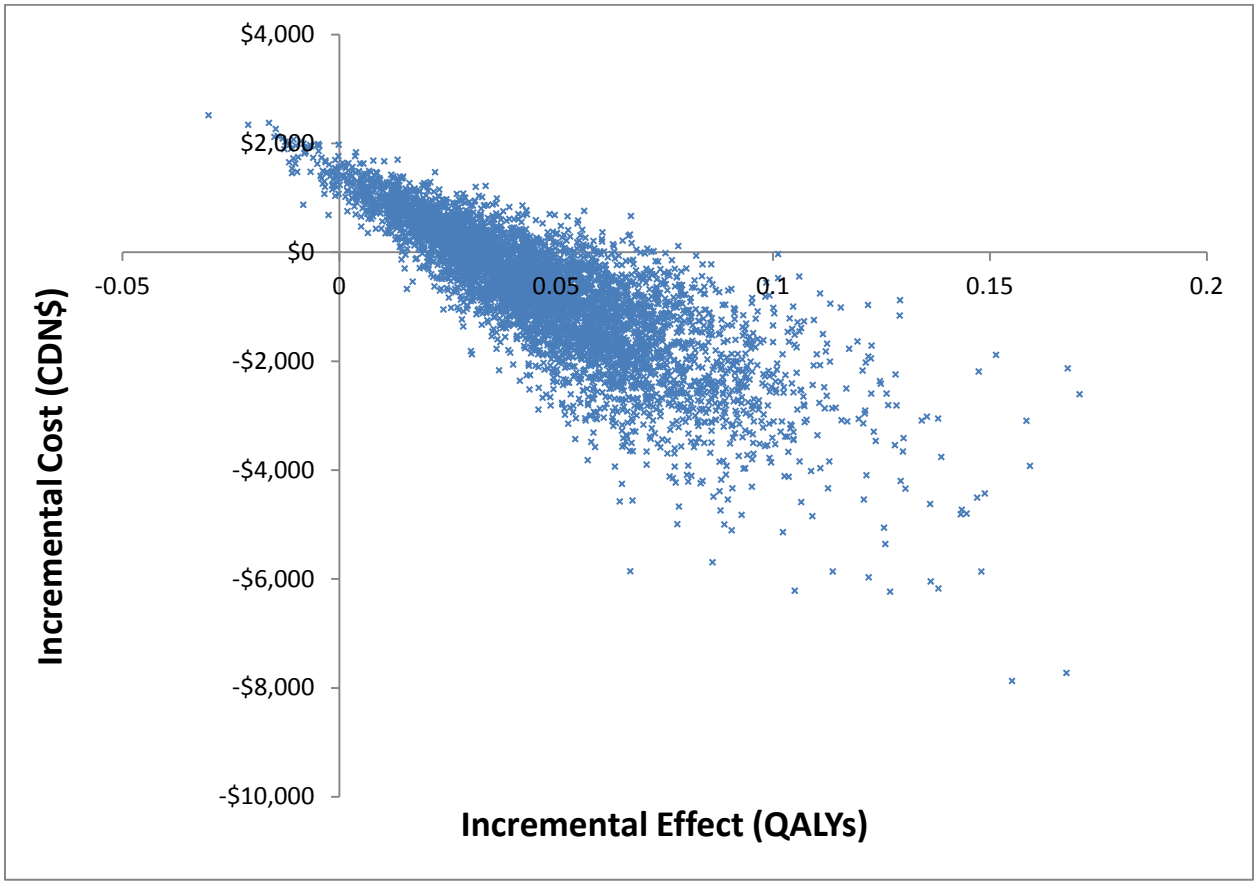


Figure 4 Incremental Cost Effectiveness Plane for ICS+LABA versus ICS

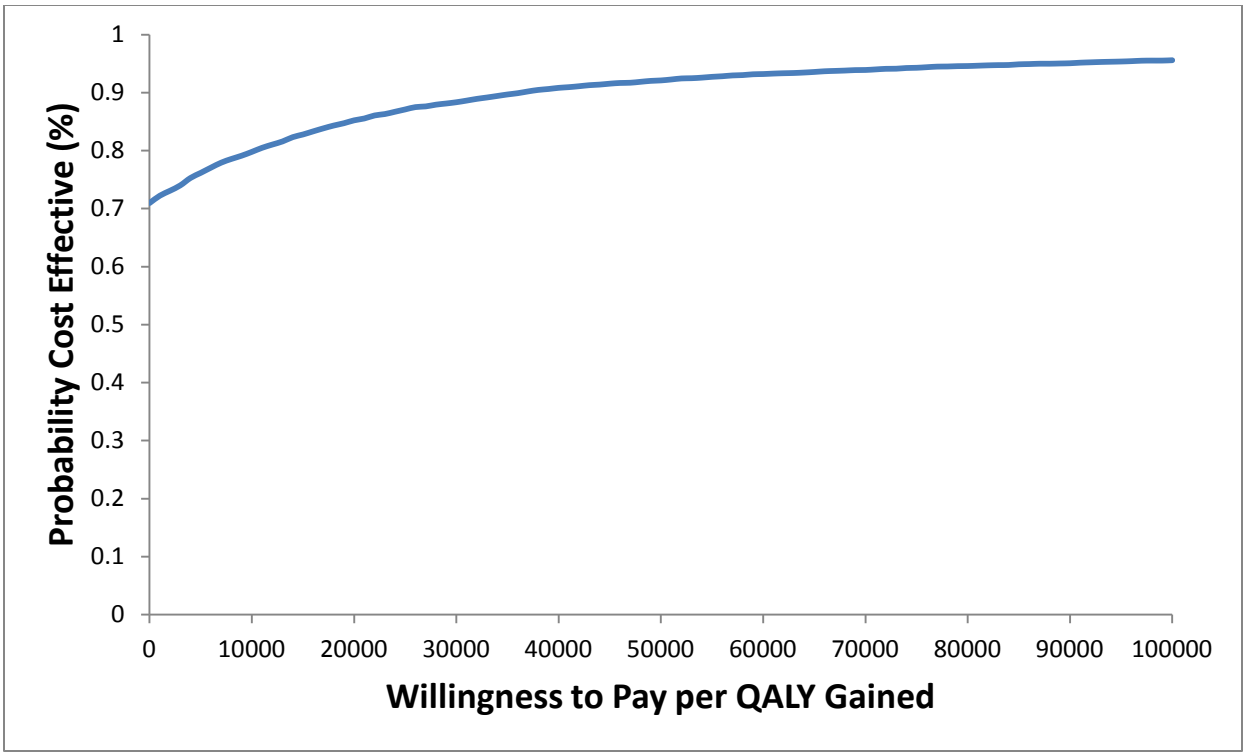


Figure 5 Cost Effectiveness Acceptability Curve for ICS+LABA versus ICS

The third objective related to the comparative cost effectiveness of triple therapy with ICS+LABA and LAMA versus both LAMA alone and the combination of LAMA and LABA.

As compared with LAMA therapy, triple therapy was more effective in 83% of simulations and more costly in 100% of simulations (Figure 6). At a willingness to pay of $50,000 per QALY, LAMA alone therapy was more cost effective in 99.9%% of simulations (Figure 7).

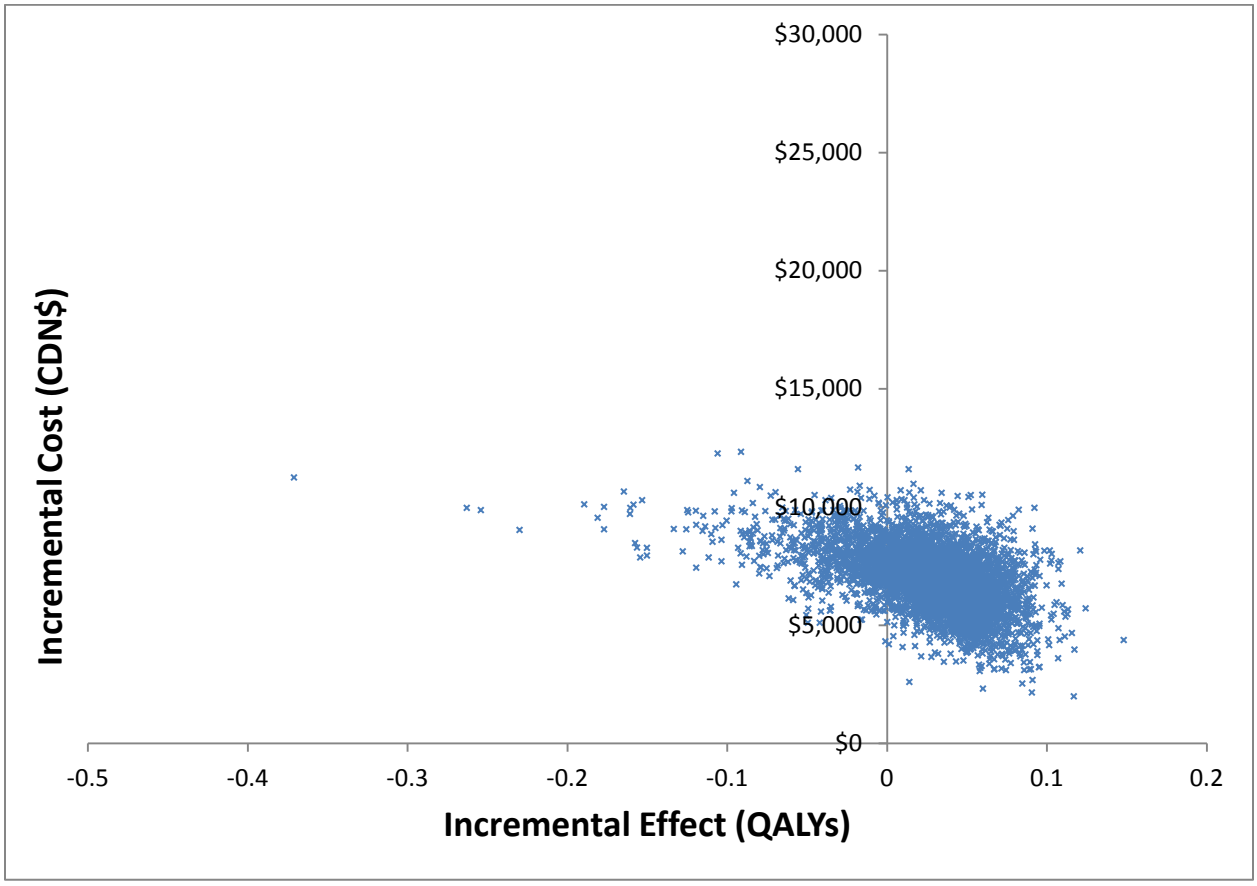


Figure 6 Incremental Cost Effectiveness Plane for Triple Therapy with ICS+LABA with LAMA versus LAMA

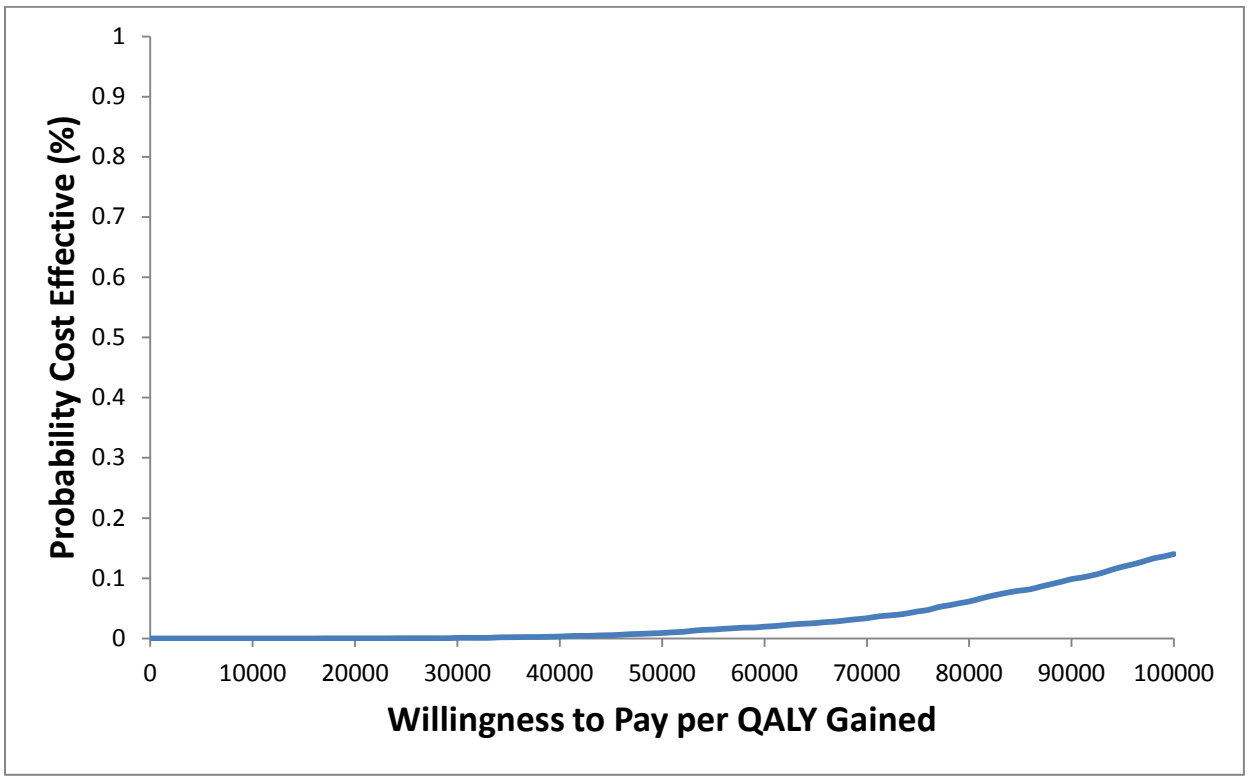


Figure 7 Cost Effectiveness Acceptability Curve for Triple Therapy with ICS+LABA with LAMA versus LAMA

Finally, when triple therapy with ICS+LABA and LAMA was compared with the combination of LAMA and LABA, triple therapy was more effective in 82% of simulations but also more costly in 81% of simulations (Figure 8). At a willingness to pay of $50,000 per QALY, triple therapy had a 53% probability of being the more cost effective strategy (Figure 9). This result should be considered in context given that LAMA and LABA taken together as single inhalers was dominated by LAMA alone.

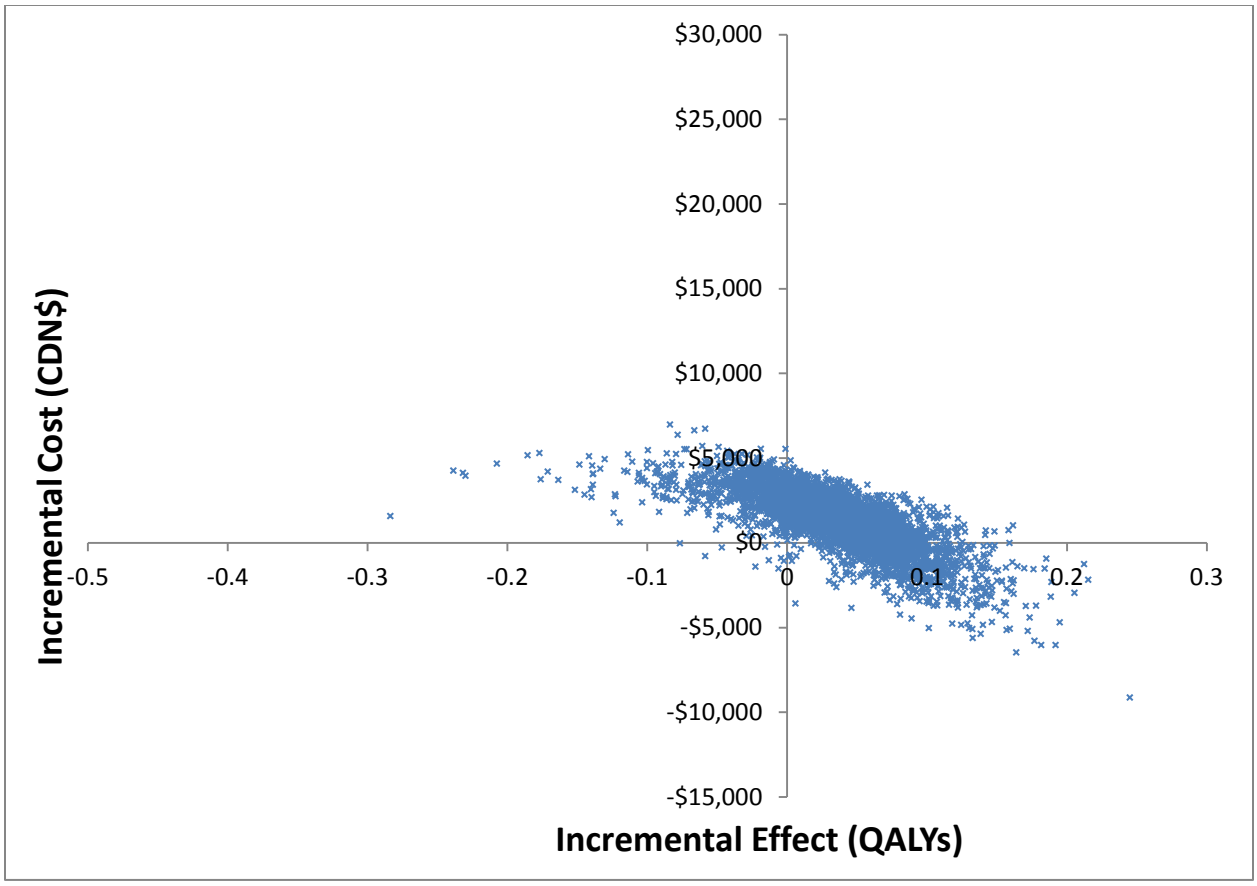


Figure 8 Incremental Cost Effectiveness Plane for Triple Therapy with ICS+LABA with LAMA versus LAMA+LABA

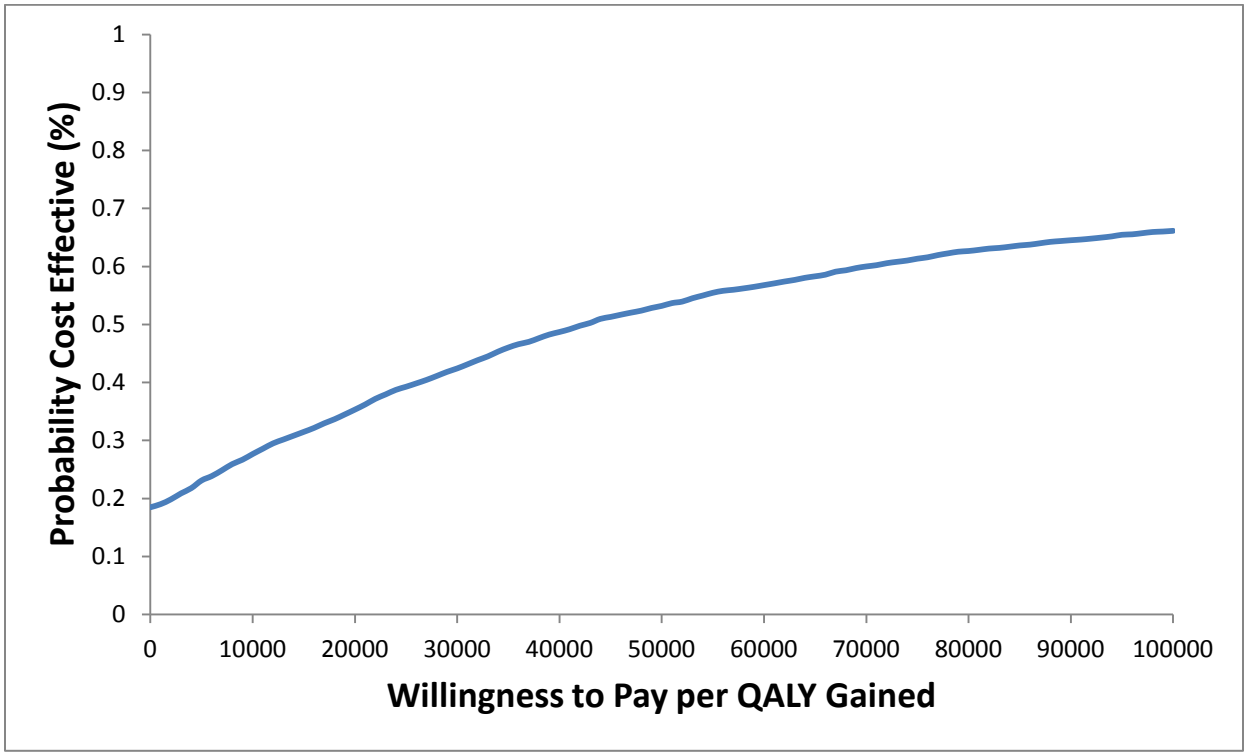


Figure 9 Cost Effectiveness Acceptability Curve for Triple Therapy with ICS+LABA with LAMA versus LAMA+LABA

Overall Summary

In comparing the cost effectiveness of ICS+LABA combination therapy administered via a single inhaler versus ICS and LABA administered via separate inhalers, the cost minimization analysis supports the cost effectiveness of combination therapy administered via a single inhaler.

With respect to the cost effectiveness of ICS+LABA combination therapy as compared with LABA alone, the combination was both more costly and more effective. Based on the incremental cost effectiveness ratio, however, for the ICS+LABA combination therapy to be considered cost effective a decision maker would have to be willing to pay more than $50,000 per QALY. Although ICS+LABA combination therapy dominated therapy with ICS alone, being both less costly and more effective, ICS alone compared with no treatment would not be considered cost effective at a threshold of $50,000 per QALY and therefore, the more appropriate comparator in this case is LABA therapy alone.

Finally, when comparing triple therapy of ICS+LABA combination therapy in addition to a LAMA with therapy with a LAMA alone, the triple therapy was both more costly than the LAMA and more effective. In no scenario, however, was the incremental cost effectiveness ratio for triple therapy versus LAMA less than $50,000 per QALY. Although triple therapy in many subgroups dominated therapy with LAMA+LABA, being both less costly and more effective, before making the decision regarding the relative cost effectiveness of triple therapy versus LAMA+LABA therapy, the cost effectiveness of LAMA+LABA therapy as compared with either agent alone should be considered. In general, LAMA alone

dominated LAMA+LABA therapy being both more effective and less costly. With respect to single therapy with a LABA, the incremental cost effectiveness ratio as compared with triple therapy was typically over one million dollars per QALY.

There are a number of limitations to this analysis primarily driven by the lack of available data. First, the purpose of the analysis was not to compare the existing ICS+LABA combination therapies given that they are not currently listed for reimbursement for COPD, rather to make inferences over the reimbursement strategies for this class. As the definition of exacerbations was inconsistent between the studies of Advair and Symbicort, it was not deemed appropriate to assess their relative cost effectiveness without further head to head trials demonstrating any differences in exacerbation rates.

Secondly, the focus of this review was the cost effectiveness of ICS+LABA combination therapies. Results relating to LAMA or LAMA+LABA combination therapies will be addressed in in a future class review.

Finally, the nature of COPD requires that only one outcome (in this case, exacerbations) can be modeled at a time without leading to the double counting of benefits. If the network meta-analysis was expanded to include FEV1% as an outcome, it would have been appropriate to re-run the economic model focusing on change ion FEV1% as the outcome of interest.

Conclusions

In patients receiving ICS and LABA via separate inhalers, this analysis supports the cost effectiveness of moving to administration of the combination via a single inhaler.

This analysis did not, however, find the combination product of ICS and LABA to be cost effective when compared with LABA alone. Additionally, the analysis did not find triple therapy with ICS+LABA combination in additional to LAMA cost effective when compared with LAMA alone.

Appendix B1 – Data Estimates

INPUT	DATA	VALUE (SE/95% CI)	DISTRIBUTION	SOURCE
Progression				
Mean FEV_1 at start of model	Moderate Severe	65% 40%		Mid-point of range in GOLD guidelines[1]
Annual decline in FEV_1		0.052 (0.029)	Normal	[125]
Monthly probability of progression	Moderate to severe Severe to very severe	0.0088 0.0132	Derived Derived	
Exacerbations per year	Moderate Severe Very severe	0.82 (0.03) 1.24 (0.03) 1.79 (0.07)	Gamma Gamma Gamma	[127]
Proportion of exacerbations requiring hospitalization	Moderate Severe Very severe	0.06 (0.02) 0.08 (0.02) 0.09 (0.04)	Beta Beta Beta	[128]
Mortality RR vs gen pop	Moderate Severe Very severe	1.50 (0.64) 3.10 (0.68) 5.02 (0.83)		[129]
Mortality with hospital exacerbation	40-49 years 50-59 years 60-69 years 70-79 years 80-89 years 90+ years	0.015 (0.009) 0.031 (0.006) 0.052 (0.005) 0.070 (0.004) 0.117 (0.006) 0.201 (0.024)	Beta Beta Beta Beta Beta Beta	[131]
Utilities				
COPD utility	Moderate Severe Very severe	0.7551 (0.0309) 0.7481 (0.0352) 0.5493 (0.0591)	Beta Beta Beta	[135,151]
QALY loss due to exacerbation	Community exacerbation Hospital exacerbation	0.1075 (0.0134) 0.3933 (0.072)	Normal Normal	[141,142]
Costs				
Drug costs (annual)	Budesonide Fluticasone Beclomethasone Formoterol Salmeterol Tiotropium	$538.79 $1119.90 $979.19 $623.99 $772.47 $889.43	Fixed	[152]

	Budesonide/formoterol Fluticasone/salmeterol Mometasone/formoterol	$1124.63 $1315.55 $1448.79		
Exacerbation costs	Community exacerbation Hospital exacerbation	$721 (180) $10757 (2689)	Gamma Gamma	[132,147,153]
Maintenance (costs/year) excluding exacerbations	Moderate COPD Severe COPD Very severe COPD	$174 (43.5) $709 (177.2) $844 (210.9)	Gamma Gamma Gamma	
Relative Treatment Effects				
Relative risk of exacerbations	Budesonide Fluticasone Formoterol Salmeterol Tiotropium Budesonide/formoterol Fluticasone/salmeterol Mometasone/formoterol Beclomethasone/formoterol Tiotropium/formoterol Tiotropium/salmeterol Tiotropium/budesonide/formoterol Tiotropium/fluticasone/salmeterol	Censored for publication	Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal	Network meta-analysis
Adverse Events – Pneumonia				
Treatment Costs	Community Hospital	$183.85 $6147.93		[150]
Disutility	Community Hospital	0.006 QALYs 0.008 QALYs		[149]
Probability of hospitalization		23.7%		[150]
Mortality rate for hospitalized pneumonia		12.93%		[150]
Relative risk of pneumonia	Budesonide Fluticasone Formoterol Salmeterol Tiotropium Budesonide/formoterol Fluticasone/salmeterol Mometasone/formoterol Beclomethasone/formoterol Tiotropium/budesonide/formoterol Tiotropium/fluticasone/salmeterol	Censored for publication	Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal Log Normal	Network meta-analysis

Figures in parenthesis are standard errors for data characterized by gamma, beta and normal distributions and 95% CI for data characterized by log-normal distributions.

Appendix C – Budget Impact Analysis

Research Question

RQ3. What is the economic impact of alternative policies for reimbursing ICS in combination with LABA for chronic treatment of COPD?

Reimbursement Based Economic Assessment

An applied, policy oriented economic model focusing on financial impact was created to facilitated consideration of alternative reimbursement strategies for COPD therapy. The analysis utilized OPDP data on usage of ICS, LABA, LAMA, and ICS+LABA from April 2011 to March 2012. COPD patients who were dispensed at least one prescription for a COPD therapy (LABA, LAMA, ICS, ICS+LABA) in Ontario were included in the analysis. The model was developed within Microsoft Excel.

First, COPD therapies were defined. COPD therapies were defined as follows:

Table 5 COPD Therapy Details

COPD Therapy	Details
Multiple Prescriptions	Multiple prescriptions dispensed during period of continuous use
Triple therapy (combo)	If overlap between ICS+LABA combo product and LAMA for minimum 30 days
Triple therapy (dual)	If overlap between all three of ICS + LAMA+LABA for minimum 30 days
Combination therapy	If use of ICS+LABA combination product
Dual therapy	(a) If overlap between ICS + LABA for minimum 30 days (b) If overlap between ICS + LAMA for minimum 30 days (c) If overlap between LAMA+LABA for minimum 30 days
Single therapy	(a) If use of ICS (b) If use of LABA (c) If use of LAMA
Single Prescription	Period of continuous use consists of only a single prescription
Single prescription – single therapy	If duration of period of continuous use is 0 days (i.e. patient only received a single prescription) (a) If prescription was for ICS (b) If prescription was for LABA (c) If prescription was for LAMA (d) If prescription was for ICS+LABA combination product
Single prescription – multiple therapy	If multiple prescriptions are dispensed on the same day, where duration of period of continuous use for each prescription is 0 days (a) If prescription for ICS+LABA combo + LAMA (b) If prescription for ICS + LAMA+LABA (c) If prescription for ICS + LABA (d) If prescription for ICS + LAMA (e) If prescription for LAMA+LABA

Then, assumptions for the analysis were specified. Assumptions for the budget impact analysis were the following:

Table 6 Budget Impact Analysis Assumptions

Assumptions
Users of combination therapy remain on current combination therapy.
A proportion of users on triple therapy (ICS and LABA and LAMA) or dual therapy (ICS and LABA) move to combination therapy.
Users of single therapy or dual therapy which does not include both LABA and ICS remain on current therapies.
Use of combination therapy in terms of number of prescription, number of users, and number of units remain the same as for ICS for SYMBICORT.
For those moving to combination products the volume of use is based on current use of ICS.

Additional details regarding the budget impact analysis can be found in Appendix C1– Model Details.

Afterwards, alternative approaches to reimbursement of COPD therapy were identified. Strategies considered included moving 20% of users on triple therapy (dual) and dual therapy (ICS and LABA) to combination product (ICS+LABA), to Advair Diskus, and to Symbicort for three COPD severity populations –Very Severe, At Least Severe, and At Least Moderate.

Table 7 Reimbursement Strategies

	REIMBURSEMENT STRATEGY	ASSUMED IMPACT
	COMBO MOVE TO LU:	
LU1	Very Severe	Current users with very severe COPD on triple therapy (dual) or dual therapy (ICS + LABA) may move to combination therapy (ICS+LABA).
LU2	At Least Severe	Current users with very severe and severe COPD on triple therapy (dual) or dual therapy (ICS + LABA) may move to combination therapy (ICS+LABA).
LU3	At Least Moderate	Current users with very severe, severe, and moderate COPD on triple therapy (dual) or dual therapy (ICS + LABA) may move to combination therapy (ICS+LABA).
	AdDisk1 under LU:	
LU4A	Advair Diskus under LU for At Least Moderate	Current users with very severe, severe, and moderate COPD on triple therapy (dual) or dual therapy (ICS + LABA) may move to Advair Diskus.
LU5A	Advair Diskus under LU for At Least Severe	Current users with very severe and severe COPD on triple therapy (dual) or dual therapy (ICS + LABA) may move to Advair Diskus.
LU6A	Advair Diskus under LU for Very Severe	Current users with very severe COPD on triple therapy (dual) or dual therapy (ICS + LABA) may move to Advair Diskus.
	Symb1 under LU:	
LU4S	Symbicort under LU for At Least Moderate	Current users with very severe, severe, and moderate COPD on triple therapy (dual) or dual therapy (ICS + LABA) may move to Symbicort.

	REIMBURSEMENT STRATEGY	ASSUMED IMPACT
LU5S	Symbicort under LU for At Least Severe	Current users with very severe and severe COPD on triple therapy (dual) or dual therapy (ICS + LABA) may move to Symbicort.
LU6S	Symbicort under LU for Very Severe	Current users with very severe COPD on triple therapy (dual) or dual therapy (ICS + LABA) may move to Symbicort.
	AdDisk2 under LU:	
LU7A	Advair Diskus under LU for At Least Moderate, Symbicort under EAP for At Least Moderate	Current users with very severe, severe, and moderate COPD on triple therapy (dual) or dual therapy (ICS + LABA) not using Pulmicort may move to Advair Diskus. Those on Pulmicort may move to Symbicort.
LU8A	Advair Diskus under LU for At Least Severe, Symbicort under EAP for At Least Severe	Current users with very severe and severe COPD on triple therapy (dual) or dual therapy (ICS + LABA) not using Pulmicort may move to Advair Diskus. Those on Pulmicort may move to Symbicort.
LU9A	Advair Diskus under LU for Very Severe, Symbicort under EAP for Very Severe	Current users with very severe COPD on triple therapy (dual) or dual therapy (ICS + LABA) not using Pulmicort may move to Advair Diskus. Those on Pulmicort may move to Symbicort.
	Symb2 under LU:	
LU7S	Symbicort under LU for At Least Moderate, Advair Diskus under EAP for At Least Moderate	Current users with very severe, severe, and moderate COPD on triple therapy (dual) or dual therapy (ICS + LABA) not using Flovent Diskus may move to Symbicort. Those on Flovent Diskus may move to Advair Diskus.
LU8S	Symbicort under LU for At Least Severe, Advair Diskus under EAP for At Least Severe	Current users with very severe and severe COPD on triple therapy (dual) or dual therapy (ICS + LABA) not using Flovent Diskus may move to Symbicort. Those on Flovent Diskus may move to Advair Diskus.
LU9S	Symbicort under LU for Very Severe, Advair Diskus under EAP for Very Severe	Current users with very severe COPD on triple therapy (dual) or dual therapy (ICS + LABA) not using Flovent Diskus may move to Symbicort. Those on Flovent Diskus may move to Advair Diskus.

For **LU1** - Combo Move to LU for Very Severe, costs were estimated by assuming 20% of current users with very severe COPD on triple therapy (dual) or dual therapy (ICS + LABA) move to combination therapy (ICS+LABA).

For **LU2** - Combo Move to LU for At Least Severe, the same approach as **LU1** was adopted with the addition of users with severe COPD.

For **LU3** - Combo Move to LU for At Least Moderate, the same approach as **LU1** was adopted with the addition of users with severe and moderate COPD.

For **LU4** - Single Combo (AdDisk1**(A)** or Symb1**(S)**) move to LU for At Least Moderate, costs were estimated by assuming 20% of current users with very severe, severe, and moderate COPD on triple therapy (dual) or dual therapy (ICS + LABA) move to either Advair Diskus or Symbicort as the preferred product, while other products are not covered.

For **LU5** – Single Combo (AdDisk1**(A)** or Symb1**(S)**) move to LU for At Least Severe, the same approach as **LU4** was adopted, however, restricted to users with very severe and severe COPD.

For **LU6** – Single Combo (AdDisk1**(A)** or Symb1**(S)**) move to LU with Very Severe, the same approach as **LU4** was adopted, however, restricted to users with very severe COPD.

For **LU7 –** Single Combo (AdDisk1**(A)** or Symb1**(S)**) move to LU and other to EAP for At Least Moderate, costs were estimated by assuming 20% of current users with very severe, severe, and moderate COPD on Alvesco and QVAR triple therapy (dual) or dual therapy (ICS + LABA) move to either Advair Diskus or Symbicort as the preferred product, while 20% of current dual or triple therapy users of Flovent and Pulmicort move to the related combination therapy (Advair Diskus and Symbicort respectively).

For **LU8 –** Single Combo (AdDisk1**(A)** or Symb1**(S)**) move to LU and other to EAP for At Least Severe, the same approach as **LU7** was adopted, however, restricted to users with very severe and severe COPD.

For **LU9 –** Single Combo (AdDisk1**(A)** or Symb1**(S)**) move to LU and other to EAP with Very Severe, the same approach as **LU7** was adopted, however, restricted to users with very severe COPD.

Then, budget expenditure on COPD therapy for each alternative strategy was forecasted. Given the scope of the drug class review, aggregated COPD therapy expenditure and usage include ICS+LABA products in inhaled aerosol and inhaled powder form, while disaggregated ICS+LABA expenditure and usage data is restricted to inhaled powder.

Findings

Current Usage and Expenditure

Table 8 COPD Therapy Users by Severity

	Users N(%)			
	ALL	VERY SEVERE	SEVERE	MODERATE
Total	205,825	30,600	28,707	146,518
Multiple Prescription				
Combination therapy	46,943(23%)	5,828(19%)	7,342(26%)	33,773(23%)
Dual therapy ICS + LABA	886(0%)	98(0%)	147(1%)	641(0%)
Dual therapy ICS + LAMA	5,858(3%)	931(3%)	887(3%)	4,040(3%)
Dual therapy LAMA+LABA	935(0%)	217(1%)	101(0%)	617(0%)
Single therapy ICS	18,928(9%)	1,444(5%)	2,421(8%)	15,063(10%)
Single therapy LABA	668(0%)	95(0%)	76(0%)	497(0%)
Single therapy LAMA	24,985(12%)	2,802(9%)	2,459(9%)	19,724(13%)
Triple therapy ICS+LABA combo	48,828(24%)	13,638(45%)	8,810(31%)	26,380(18%)
Triple therapy dual	731(0%)	191(1%)	130(0%)	410(0%)
Single Prescription				
Combination therapy	27,497(13%)	3,025(10%)	3,455(12%)	21,017(14%)
Multiple therapy - ICS+LABA combo + LAMA	3,091(2%)	518(2%)	357(1%)	2,216(2%)
Single therapy – ICS	16,267(8%)	790(3%)	1,504(5%)	13,973(10%)
Multiple therapy - ICS + LABA	81(0%)	≤5(0%)	8(0%)	73(0%)
Multiple therapy - ICS + LAMA+LABA	12(0%)	≤5(0%)	≤5(0%)	12(0%)
Multiple therapy - ICS + LAMA	596(0%)	57(0%)	79(0%)	460(0%)
Single therapy – LABA	189(0%)	22(0%)	20(0%)	147(0%)
Multiple therapy - LAMA+LABA	42(0%)	6(0%)	≤5(0%)	36(0%)
Single therapy – LAMA	9,288(5%)	938(3%)	911(3%)	7,439(5%)

Total number of users was 205,825; patients with moderate COPD accounted for the greatest number of users (accounting for 71% of users).

Summary of Findings for Table 8

1. Total COPD therapy users were 205,825, ranging from 28,707 users with severe COPD to 146,518 users with moderate COPD.
2. Users of Triple therapy ICS+LABA combo with multiple prescription accounted for 45% of patients with very severe COPD, while users of Combination therapy accounted for 19%.
3. Users of Triple therapy ICS+LABA combo with multiple prescription accounted for 31% of patients with severe COPD, while users of Combination therapy accounted for 26%.
4. Users of Combination therapy with multiple prescription accounted for 23% of patients with moderate COPD, while users of Triple therapy ICS+LABA combo accounted for 18%.

Table 9 COPD Therapy Units by Severity

	UNITS* N(%)			
	ALL	**VERY SEVERE**	**SEVERE**	**MODERATE**
COPD Therapy	108,115,920	20,514,920	17,770,670	69,830,330
ICS	21,786,000(20%)	2,189,780(11%)	2,966,480(17%)	16,629,740(24%)
LABA	1,546,200(1%)	287,460(1%)	219,780(1%)	1,038,960(1%)
LAMA	20,847,660(19%)	4,636,500(23%)	3,226,170(18%)	12,984,990(19%)
ICS+LABA**	63,936,060(59%)	13,401,180(65%)	11,358,240(64%)	39,176,640(56%)
ADVAIR DISKUS 100MCG	364,560(0%)	42,180(0%)	44,520(0%)	277,860(0%)
ADVAIR DISKUS 250MCG	12,482,880(12%)	2,333,520(11%)	1,896,000(11%)	8,253,360(12%)
ADVAIR DISKUS 500MCG	8,303,340(8%)	2,424,480(12%)	1,651,560(9%)	4,227,300(6%)
SYMBICORT 100MCG	749,400(1%)	112,800(1%)	115,800(1%)	520,800(1%)
SYMBICORT 200MCG	24,583,560(23%)	4,176,240(20%)	4,597,560(26%)	15,809,760(23%)

UNITS* = per puff

ICS+LABA** = includes inhaled aerosol and powder form

Total COPD therapy units were 108.1 million; ICS+LABA accounted for 59% of units, while ICS, LABA, and LAMA individually accounted for 20% or less.

Summary of Findings for Table 9

1. Total COPD therapy units were 108.1 million, the number of units ranged from 17.8 million for patients with severe COPD to 69.8 million for patients with moderate COPD.
2. For patients with very severe and severe COPD, ICS+LABA accounted for the greatest number of units (13.4 million and 11.4 million respectively), followed by LAMA (4.6 million and 3.2 million).
3. For patients with moderate COPD, ICS+LABA accounted for the greatest number of units (39.2 million), followed by ICS (16.6 million).
4. Of the inhaled powder ICS+LABA products, SYMBICORT 200MCG accounted for the largest percentage of units.

Table 10 Percentage of ICS+LABA Units by Severity

	ICS+LABA UNITS* %**			
	ALL	**VERY SEVERE**	**SEVERE**	**MODERATE**
ADVAIR DISKUS 100MCG	1%	0%	0%	1%
ADVAIR DISKUS 250MCG	20%	17%	17%	21%
ADVAIR DISKUS 500MCG	13%	18%	15%	11%
SYMBICORT 100MCG	1%	1%	1%	1%
SYMBICORT 200MCG	38%	31%	40%	40%

ICS+LABA UNITS* = per puff

%** = denominator based on inhaled aerosol and powder form

SYMBICORT 200MCG accounted for 38% of ICS+LABA units, while ADVAIR DISKUS 250MCG accounted for 20% of ICS+LABA units.

Summary of Findings for Table 10

1. For patients with very severe, severe, and moderate COPD, SYMBICORT 200MCG accounted for the greatest percentage of ICS+LABA units.
2. ADVAIR DISKUS 100MCG accounted for the smallest percentage of ICS+LABA units for patients with very severe and severe COPD.
3. Both ADVAIR DISKUS 100MCG and SYMBICORT 100MCG accounted for the smallest percentage of ICS+LABA units for patients with moderate COPD.

Table 11 Number of Prescriptions by Severity

	PRESCRIPTIONS N			
	ALL	**VERY SEVERE**	**SEVERE**	**MODERATE**
COPD Therapy	1,075,744	221,093	173,332	681,319
ICS	137,713	13,998	18,864	104,851
LABA	16,860	3,226	2,409	11,225
LAMA	402,955	93,379	61,988	247,588
ICS+LABA*	518,216	110,490	90,071	317,655
ADVAIR DISKUS 100MCG	4,240	529	526	3,185
ADVAIR DISKUS 250MCG	148,828	28,303	22,646	97,879
ADVAIR DISKUS 500MCG	99,061	28,801	19,599	50,661
SYMBICORT 100MCG	4,796	724	697	3,375
SYMBICORT 200MCG	147,049	24,255	26,927	95,867

ICS+LABA* = includes inhaled aerosol and powder form

The most commonly prescribed COPD therapy was ICS+LABA across all patients and COPD severity.

Summary of Findings for Table 11

1. The most commonly prescribed COPD therapy was ICS+LABA, followed by LAMA, while LABA was the least prescribed therapy across all patients.
2. Of the inhaled powder ICS+LABA products, the most frequent prescription was ADVAIR DISKUS 500 MCG for patients with very severe COPD, SYMBICORT 200MCG for patients with severe COPD, and ADVAIR DISKUS 250MCG for patients with moderate COPD.

Table 12 Total COPD Therapy Expenditure by Severity

	TOTAL COPD THERAPY EXPENDITURE IN 2012 $ (%)			
	ALL	**VERY SEVERE**	**SEVERE**	**MODERATE**
COPD Therapy	$141,599,030	$30,407,819	$23,612,903	$87,578,309
ICS	$12,462,252 (9%)	$1,346,254 (4%)	$1,767,658 (7%)	$9,348,340 (11%)
LABA	$1,447,155 (1%)	$274,033 (1%)	$204,485 (1%)	$968,637 (1%)
LAMA	$47,132,103 (33%)	$10,530,481 (35%)	$7,323,341 (31%)	$29,278,280 (33%)
ICS+LABA*	$80,557,521 (57%)	$18,257,051 (60%)	$14,317,418 (61%)	$47,983,052 (55%)
ADVAIR DISKUS 100MCG	$523,877 (0%)	$61,517(0%)	$64,091 (0%)	$398,269 (0%)
ADVAIR DISKUS 250MCG	$21,632,228 (15%)	$4,081,846(13%)	$3,292,553 (14%)	$14,257,830 (16%)
ADVAIR DISKUS 500MCG	$20,454,900 (14%)	$5,992,029(20%)	$4,068,330 (17%)	$10,394,540 (12%)
SYMBICORT 100MCG	$414,719 (0%)	$63,460(0%)	$63,986 (0%)	$287,273 (0%)
SYMBICORT 200MCG	$17,655,494 (12%)	$3,037,519 (10%)	$3,309,759 (14%)	$11,308,217 (13%)

ICS+LABA* = includes inhaled aerosol and powder form

In 2012, total COPD therapy expenditure by OPDP was $141.6 million for all patients, and varied from 23.6 million for patients with severe COPD to 87.6 million for patients with moderate COPD.

Summary of Findings for Table 12

1. Total COPD expenditure was $141.6 million, ranging from $1.4 million for LABA to $80.6 million for ICS+LABA.
2. Expenditure for patients with moderate COPD was the greatest, ranging from $1.0 million for LABA to 48.0 million for ICS+LABA.
3. For all users of inhaled powder ICS+LABA products, expenditure varied from $0.4 million to $21.6 million.
4. Of inhaled powder ICS+LABA products, ADVAIR DISKUS 250MCG accounted for the greatest expenditure in users with moderate COPD (accounting for 16% of total COPD expenditure), while in users with very severe and severe COPD, ADVAIR DISKUS 500MCG accounted for the greatest expenditure (accounting for 20% and 17% of total COPD expenditure respectively).

Table 13 Average Cost per Unit by Severity

	AVERAGE COST PER UNIT * $			
	ALL	VERY SEVERE	SEVERE	MODERATE
COPD Therapy	$1.31	$1.48	$1.33	$1.25
ICS	$0.57	$0.61	$0.60	$0.56
LABA	$0.94	$0.95	$0.93	$0.93
LAMA	$2.26	$2.27	$2.27	$2.25
ICS+LABA**	$1.26	$1.36	$1.26	$1.22
ADVAIR DISKUS 100MCG	$1.44	$1.46	$1.44	$1.43
ADVAIR DISKUS 250MCG	$1.73	$1.75	$1.74	$1.73
ADVAIR DISKUS 500MCG	$2.46	$2.47	$2.46	$2.46
SYMBICORT 100MCG	$0.55	$0.56	$0.55	$0.55
SYMBICORT 200MCG	$0.72	$0.73	$0.72	$0.72

AVERAGE COSTS PER UNIT*= per puff
ICS+LABA** = includes inhaled aerosol and powder form

In 2012, the average cost per unit was $1.31 and varied between $1.25 per unit for patients with moderate COPD to $1.48 per unit for patients with very severe COPD.

Summary of Findings for Table 13

- LAMA had the highest average cost per unit at $2.26 per unit, while ICS had the lowest average cost per unit at $0.57.
- The average cost per unit for ICS+LABA varied from $0.55 for SYMBICORT 100MCG to $2.46 for ADVAIR DISKUS 500MCG.

Impact of Alternative Approaches to Reimbursement

Table 14 Summary of Budget Impact

#	STRATEGY	IMPACT	TOTAL	% BUDGET IMPACT
	Current Reimbursement			
			$141,599,030	
	Combo Move to LU:			
LU1	Very Severe	Expected total $	$141,590,604	**↓ 0.006%**
		Budget impact	-$8,427	
LU2	At Least Severe	Expected total $	$141,581,490	**↓ 0.012%**
		Budget impact	-$17,540	
LU3	At Least Moderate	Expected total $	$141,550,754	**↓ 0.034%**
		Budget impact	-$48,277	
	AdDisk1 under LU:			
LU4A	At Least Moderate	Expected total $	$133,012,348	**↓6.064%**
		Budget impact	-$8,586,683	
LU5A	At Least Severe	Expected total $	$138,012,318	**↓ 2.533%**

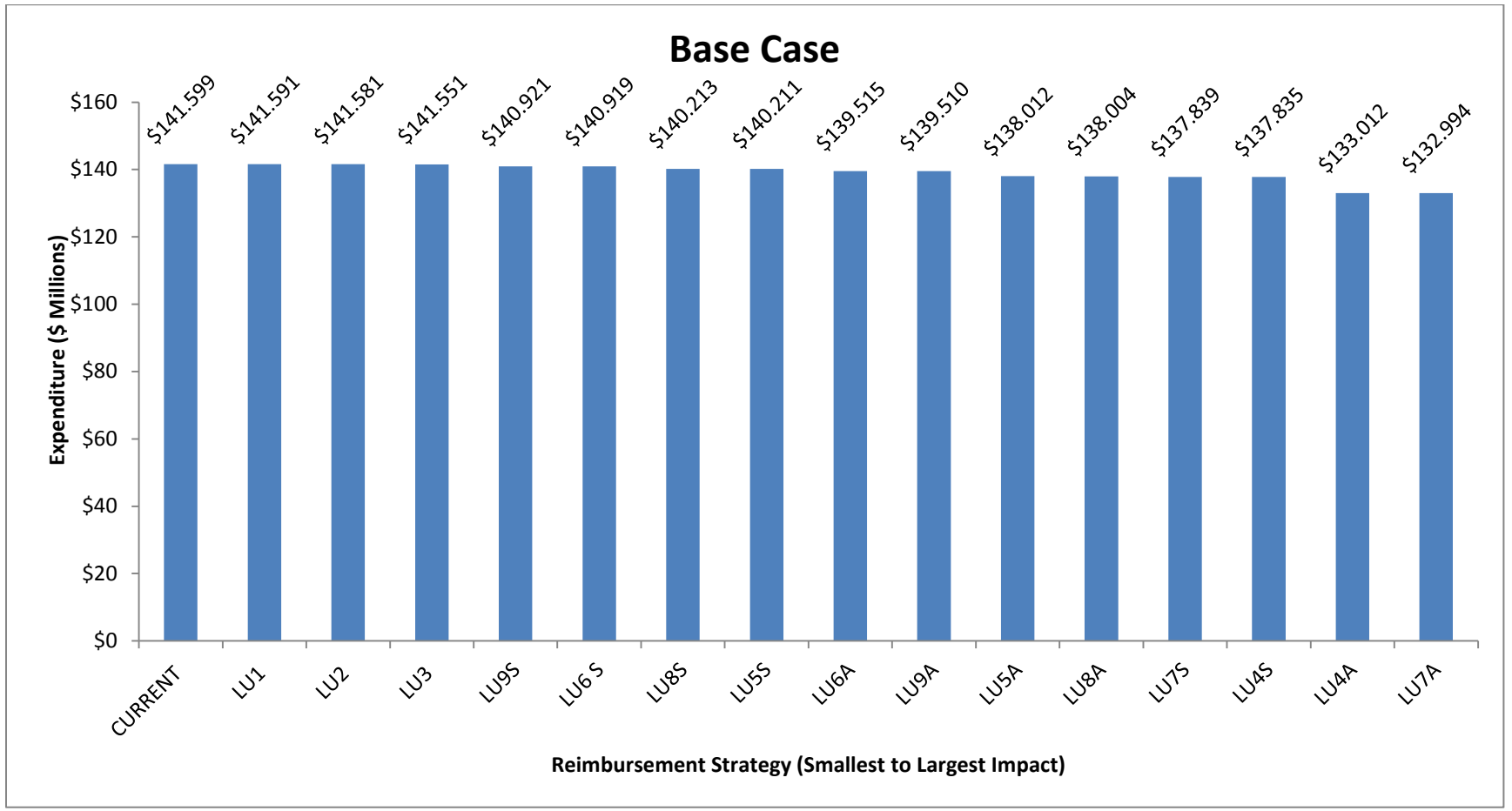
#	STRATEGY	IMPACT	TOTAL	% BUDGET IMPACT
		Budget impact	-$3,586,713	
LU6A	Very Severe	Expected total $	$139,515,062	**↓ 1.472%**
		Budget impact	-$2,083,968	
	Symb1 under LU:			
LU4S	At Least Moderate	Expected total $	$137,835,270	**↓ 2.658%**
		Budget impact	-$3,763,760	
LU5S	At Least Severe	Expected total $	$140,211,068	**↓ 0.980%**
		Budget impact	-$1,387,963	
LU6S	Very Severe	Expected total $	$140,918,740	**↓ 0.480%**
		Budget impact	-$680,291	
	AdDisk2 under LU:			
LU7A	At Least Moderate	Expected total $	$132,993,680	**↓ 6.077%**
		Budget impact	-$8,605,351	
LU8A	At Least Severe	Expected total $	$138,004,334	**↓ 2.539%**
		Budget impact	-$3,594,697	
LU9A	Very Severe	Expected total $	$139,509,802	**↓ 1.475%**
		Budget impact	-$2,089,229	
	Symb2 under LU:			
LU7S	At Least Moderate	Expected total $	$137,839,359	**↓ 2.655%**
		Budget impact	-$3,759,671	
LU8S	At Least Severe	Expected total $	$140,213,461	**↓ 0.979%**
		Budget impact	-$1,385,570	
LU9S	Very Severe	Expected total $	$140,920,784	**↓ 0.479%**
		Budget impact	-$678,246	

Disaggregated results by drug class are available in Appendix C2 – Alternative Approaches to Reimbursement Results.

Summary of Findings for Table 14

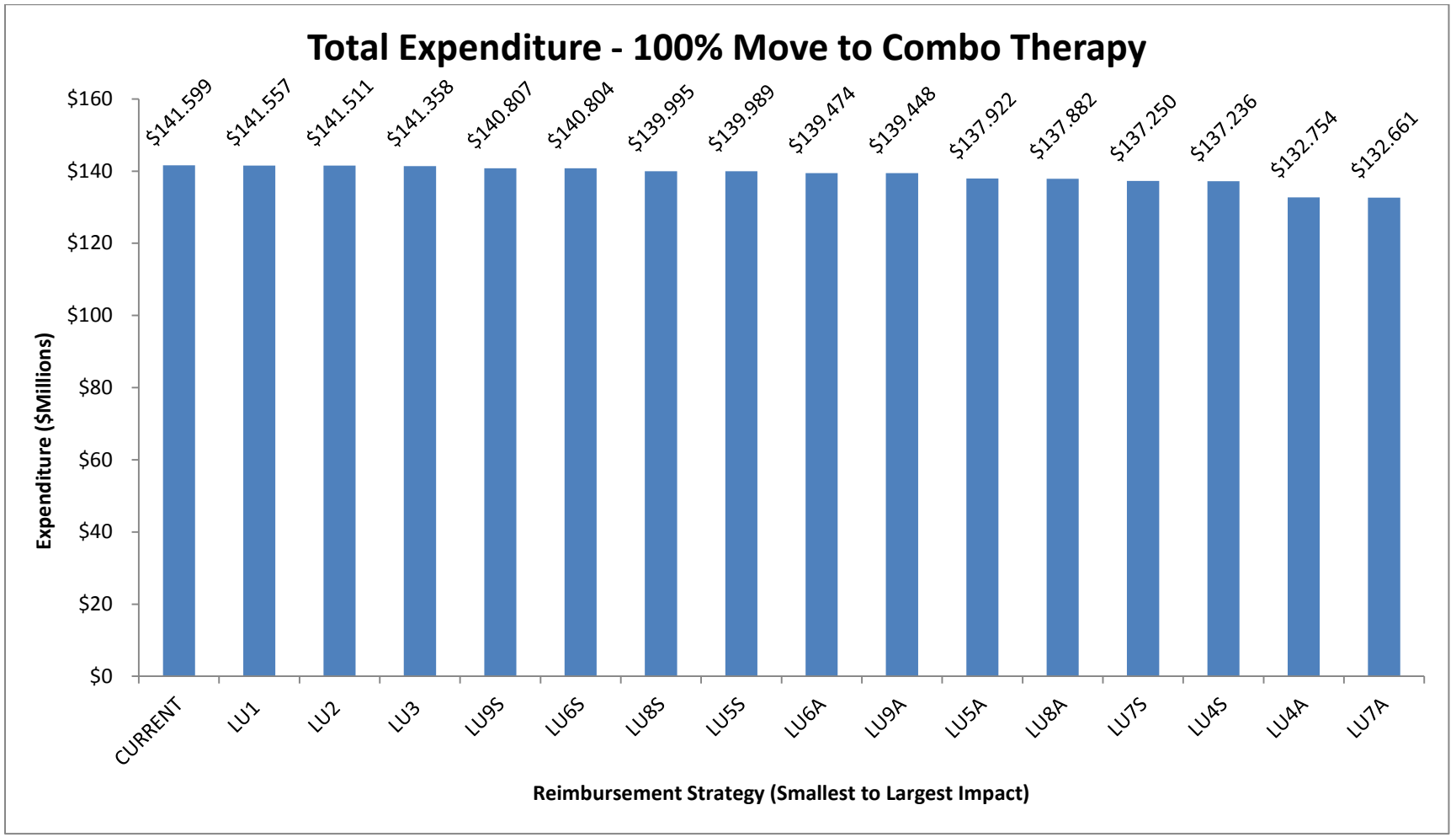
- In 2012, the total expenditure on COPD therapy (ICS, LABA, ICS+LABA, LAMA) was $141.6 million.
- Moving to LU, whereby current users with very severe COPD on triple therapy (dual) or dual therapy (ICS + LABA) move to combination therapy (ICS+LABA), will lead to a relatively small decline in total COPD therapy expenditures (a reduction of $8,427or 0.006%).
- Similarly, moving to LU, whereby current users with at least severe or at least moderate COPD on triple therapy (dual) or dual therapy (ICS + LABA) move to combination therapy (ICS+LABA), will have a slightly greater impact on total COPD therapy expenditure (a reduction of 0.012% and 0.034% respectively or a reduction of $17,540 and $48,277 respectively).
- Moving Advair Diskus to LU as the preferred product, while other products are not covered (LU4A-LU6A), would lead to a significantly greater decline in total costs ranging from 1.472%-6.064% (savings of $2.1 million for users with very severe COPD, $3.6 million for users with at least severe COPD, $8.6 million for users with at least moderate COPD). Moving Advair Diskus to LU as the preferred product, while other products are available under EAP (LU7A-LU9A), would lead to similar results.
- However, moving Symbicort to LU as the preferred product, while other products are not covered (LU4S-LU6S), would lead to a reduction in total costs ranging from 0.480%-2.658% (savings of $0.7 million for users with very severe COPD, $1.4 million for users with at least severe COPD, $3.8 million for users with at least moderate COPD). Moving Symbicort to LU as the preferred product, while other products are available under EAP (LU7S-LU9S), would lead to a similar reduction in costs.

Figure 10 Total Expenditure - Base Case



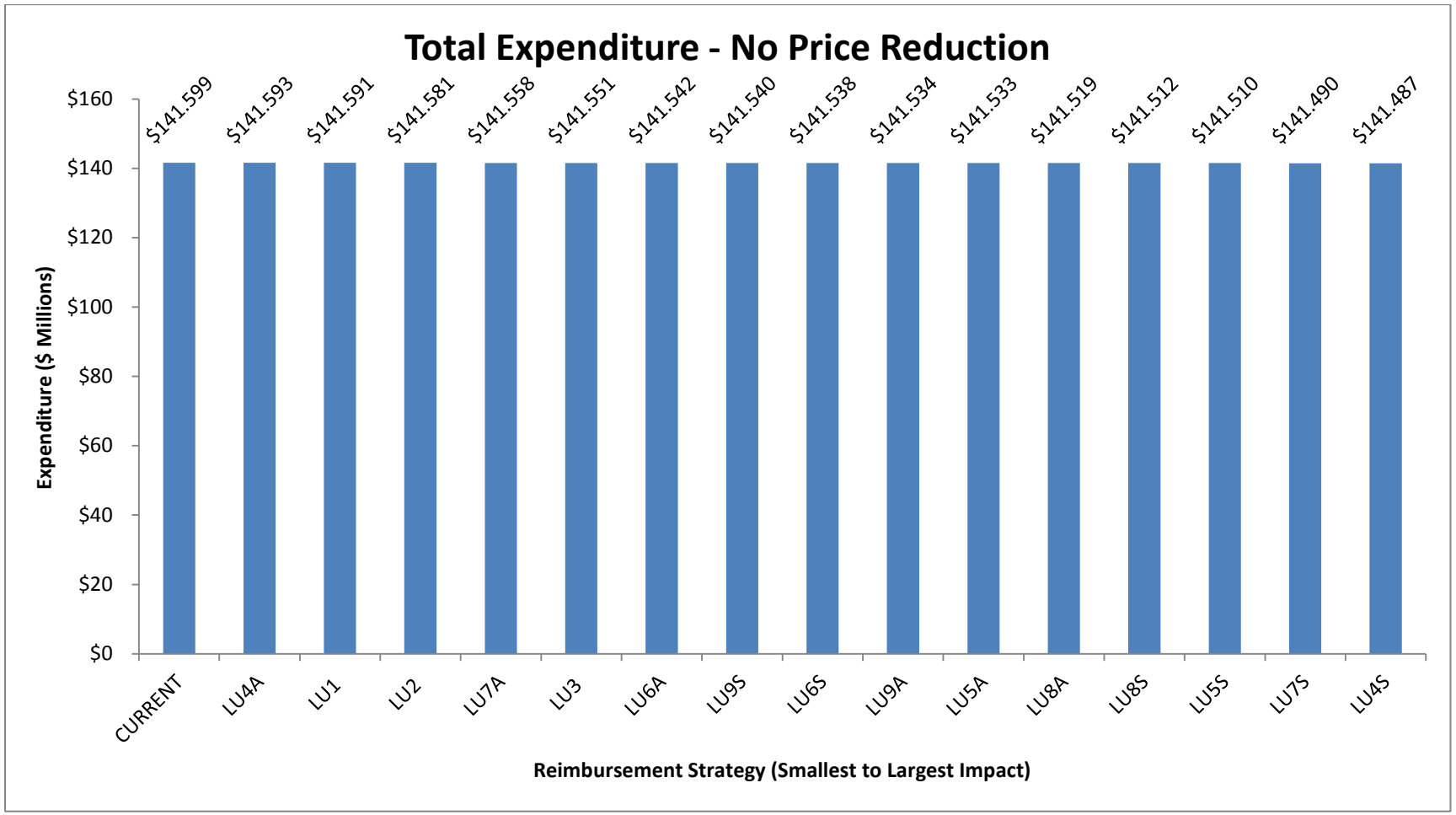
In order of least to most impact, LU1-LU3 have the smallest impact, while LU4A and LU7A have the greatest impact on COPD therapy expenditure.

Figure 11 Total Expenditure - 100% Users of Triple Therapy Dual and Dual Therapy (ICS + LABA) Move to Combination Therapy



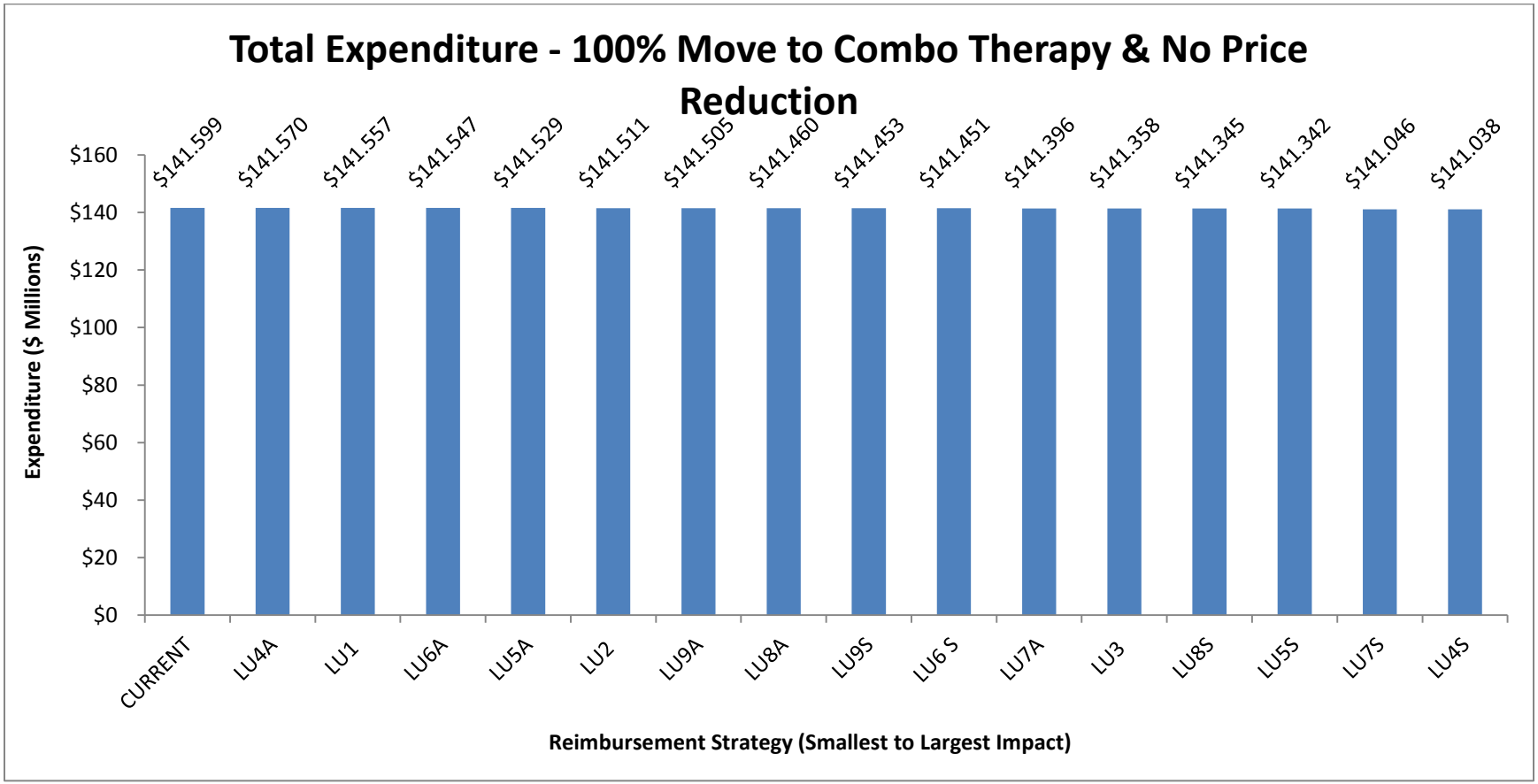
In order of least to most impact, LU1-LU3 would have the smallest impact, while LU4A and LU7A would have the greatest impact on COPD therapy expenditure if all users of triple therapy dual and dual therapy (ICS +LABA) moved to combination therapy.

Figure 12 Total Expenditure- No Price Reduction in Preferred Combination Therapy



In order of least to most impact, LU4A, LU1 and LU2 would have the smallest impact, while LU4S and LU7S would have the greatest impact on COPD therapy expenditure if there was no reduction in the costs of preferred therapy.

Figure 13 Total Expenditure - 100% Users of Triple Therapy Dual and Dual Therapy (ICS + LABA) Move to Combination Therapy and No Price Reduction in Preferred Combination Therapy



In order of least to most impact LU4A, LU1, and LU6 would have the smallest impact, while LU4S and LU7S would have the greatest impact on COPD therapy expenditure if all users of triple therapy dual and dual therapy (ICS + LABA) moved to a preferred therapy and there was no reduction in the costs of preferred therapy.

Table 15 Budget Impact - Sensitivity Analysis

#	Impact	Base Case		100% triple dual and dual (ICS + LABA) users move		No price reduction		100% triple dual and dual (ICS + LABA) users move and no price reduction	
		Total	% Budget Impact	Total	% Budget Impact	Total	% Budget Impact	Total	% Budget Impact
LU1	Expected total $	$141,590,604	**↓0.006%**	$141,556,897	**↓ 0.030%**	$141,590,604	**↓0.006%**	$141,556,897	**↓0.030%**
	Budget impact	-$8,427		-$42,134		-$8,427		-$42,134	
LU2	Expected total $	$141,581,490	**↓0.012%**	$141,511,329	**↓ 0.062%**	$141,581,490	**↓0.012%**	$141,511,329	**↓0.062%**
	Budget impact	-$17,540		-$87,701		-$17,540		-$87,701	
LU3	Expected total $	$141,550,754	**↓0.034%**	$141,357,648	**↓ 0.170%**	$141,550,754	**↓0.034%**	$141,357,648	**↓0.170%**
	Budget impact	-$48,277		-$241,383		-$48,277		-$241,383	
LU4A	Expected total $	$133,012,348	**↓6.064%**	$132,754,421	**↓ 6.246%**	$141,593,278	**↓0.004%**	$141,570,270	**↓0.020%**
	Budget impact	-$8,586,683		-$8,844,610		-$5,752		-$28,761	
LU5A	Expected total $	$138,012,318	**↓2.533%**	$137,922,029	**↓ 2.597%**	$141,532,951	**↓0.047%**	$141,528,970	**↓0.049%**
	Budget impact	-$3,586,713		-$3,677,001		-$66,080		-$70,060	

#	Impact	Base Case		100% triple dual and dual (ICS + LABA) users move		No price reduction		100% triple dual and dual (ICS + LABA) users move and no price reduction	
		Total	% Budget Impact	Total	% Budget Impact	Total	% Budget Impact	Total	% Budget Impact
LU6A	Expected total $	$139,515,062	**↓1.472%**	$139,474,082	**↓1.501%**	$141,541,989	**↓0.040%**	$141,547,044	**↓0.037%**
	Budget impact	-$2,083,968		-$2,124,949		-$57,042		-$51,986	
LU4S	Expected total $	$137,835,270	**↓2.658%**	$137,236,398	**↓ 3.081%**	$141,486,733	**↓0.079%**	$141,037,543	**↓0.397%**
	Budget impact	-$3,763,760		-$4,362,633		-$112,297		-$561,487	
LU5S	Expected total $	$140,211,068	**↓0.980%**	$139,989,466	**↓ 1.137%**	$141,509,978	**↓0.063%**	$141,341,855	**↓0.182%**
	Budget impact	-$1,387,963		-$1,609,565		-$89,053		-$257,176	
LU6S	Expected total $	$140,918,740	**↓0.480%**	$140,803,961	**↓ 0.561%**	$141,537,982	**↓0.043%**	$141,450,790	**↓0.105%**
	Budget impact	-$680,291		-$795,069		-$61,049		-$148,240	
LU7A	Expected total $	$132,993,680	**↓6.077%**	$132,661,080	**↓ 6.312%**	$141,558,474	**↓0.029%**	$141,396,249	**↓0.143%**
	Budget impact	-$8,605,351		-$8,937,950		-$40,556		-$202,782	
LU8A	Expected total $	$138,004,334	**↓2.539%**	$137,882,111	**↓2.625%**	$141,519,257	**↓0.056%**	$141,460,499	**↓0.098%**

#	Impact	Base Case		100% triple dual and dual (ICS + LABA) users move		No price reduction		100% triple dual and dual (ICS + LABA) users move and no price reduction	
		Total	% Budget Impact	Total	% Budget Impact	Total	% Budget Impact	Total	% Budget Impact
	Budget impact	-$3,594,697		-$3,716,920		-$79,774		-$138,532	
LU9A	Expected total $	$139,509,802	↓1.475%	$139,447,778	↓1.519%	$141,533,630	↓0.046%	$141,505,251	↓0.066%
	Budget impact	-$2,089,229		-$2,151,252		-$65,401		-$93,780	
LU7S	Expected total $	$137,839,359	↓2.655%	$137,250,097	↓ 3.071%	$141,489,756	↓0.077%	$141,045,910	↓0.391%
	Budget impact	-$3,759,671		-$4,348,934		-$109,274		-$553,120	
LU8S	Expected total $	$140,213,461	↓0.979%	$139,994,683	↓ 1.133%	$141,511,990	↓0.061%	$141,345,166	↓0.179%
	Budget impact	-$1,385,570		-$1,604,347		-$87,041		-$253,865	
LU9S	Expected total $	$140,920,784	↓0.479%	$140,807,436	↓ 0.559%	$141,539,813	↓0.042%	$141,453,196	↓0.103%
	Budget impact	-$678,246		-$791,595		-$59,218		-$145,834	

Summary of Findings for Figures 10-13 and Table 15

1. In 2012, COPD therapy expenditure was 141.6 million.
2. In the base case, LU4A and LU7A have the greatest impact on COPD therapy expenditure (a reduction of 6.064% and 6.077%).
3. The analysis is most sensitive to price reduction.
4. With a 20% price reduction, having a preferred product would lead to a reduction in COPD therapy costs of between 2.655% and 6.077% if applied to all with at least moderate COPD. However, if there was no reduction in the cost of the preferred product, the cost reduction would be between 0.004% and 0.079%.
5. With a preferred product, if all users of triple therapy dual and dual therapy (ICS + LABA) moved to combination therapy, the cost reduction would be between 1.137% and 6.312%. Similarly, if all users of triple therapy dual and dual therapy (ICS + LABA) moved to combination therapy and no reduction in the cost of the preferred product, the cost reduction would be between 0.02% and 0.397%.

Overall Conclusions and Summary

In 2012, the total expenditure on COPD therapy (ICS, LABA, ICS+LABA, LAMA) was $141.6 million.

Moving combination (ICS+LABA) products to LU for patients with at least moderate COPD, will lead to a small absolute decrease in total COPD therapy expenditure (a reduction of $48,277 or 0.034%).

A strategy whereby one of the combination products were listed under LU for those with at least moderate COPD based on a 20% price reduction would lead to greater absolute savings (a reduction ranging from $3.8 million to $8.6 million or 2.658% to 6.064%)

Analyses with respect to potential price reductions are illustrative. If potential price reductions were identified, this would facilitate further analysis demonstrating the budget impact of such proposals.

Analysis did not assess the budget impact of maintaining coverage as is but with increased efforts to either educate physicians on appropriate prescribing of ICS+LABA combination therapies of controlling of prescribing. Given that the benefits of these practices are unknown, it was unclear from what basis to make assumptions concerning the modeling any resultant change in prescribing.

Conclusions

Moving ICS+LABA combination products to LU will have a limited impact on COPD drug therapy expenditure. Negotiating with either the manufacturer of Symbicort or Advair Diskus to allow coverage under LU with a price reduction of 20% would lead to modest cost savings of between $3.8 million and $8.6 million assuming coverage for at least moderate disease.

Appendix C – Appendices
Appendix C1– Model Details

Move to Combination Product in LU (LU1-LU3)

In **LU1 – LU3**, for users on triple therapy (dual) and dual therapy (ICS + LABA), 20% moved to combination therapy (ICS+LABA combination product). The following assumptions for the move to combination product in LU were made:

Table 16 Assumptions for Move to Combination Product in LU (LU1-LU3)

Assumptions
Users of combination therapy remain on current combination therapy.
A proportion of users on triple therapy (dual) or dual therapy (ICS + LABA) move to combination therapy. This move is based on current ICS users (PULMICORT and FLOVENT DISKUS users, FLOVENT HFA users, and Other ICS users).
Use of combination therapy in terms of number of prescription, number of users, and number of units remain the same as for ICS for SYMBICORT.
Use of combination therapy in terms of number of prescription and number of users remain the same as for ICS for ADVAIR DISKUS, and the number of units is halved.

The following table illustrates how users on triple therapy (dual) or dual therapy (ICS + LABA) moved to combination product (ICS+LABA).

Table 17 Details of Move to Combination Product in LU (LU1-LU3)

Details of Move to Combination Product			
Users on triple therapy (dual) or dual therapy (ICS + LABA), whose initial therapy is:		**Will move to:**	
PULMICORT	200MCG	SYMBICORT	100MCG
PULMICORT	400MCG	SYMBICORT	200MCG
PULMICORT	100MCG	SYMBICORT	100MCG
FLOVENT DISKUS	250MCG	ADVAIR DISKUS	250MCG
FLOVENT DISKUS	500MCG	ADVAIR DISKUS	500MCG
QVAR	50MCG	ADVAIR DISKUS/SYMBICORT based on current usage	
QVAR	100MCG	ADVAIR DISKUS/SYMBICORT based on current usage	
FLOVENT HFA	50MCG	ADVAIR DISKUS	100MCG
FLOVENT HFA	125MCG	ADVAIR DISKUS	250MCG
FLOVENT HFA	250MCG	ADVAIR DISKUS	500MCG
ALVESCO	100MCG	ADVAIR DISKUS/SYMBICORT based on current usage	
ALVESCO	200MCG	ADVAIR DISKUS/SYMBICORT based on current usage	

The proportion of users moving to combination therapy by COPD severity was based on current usage. The following quantifies the proportion of users moving to combination therapy by COPD severity:

Table 18 Proportion of Users Moving to Combination Therapy in LU (LU1-LU3) by COPD Severity

Proportion of Users Moving to Combination Therapy by COPD Severity				
Combination therapy:		**Very Severe**	**Severe**	**Moderate**
ADVAIR DISKUS	100MCG	0.01	0.01	0.01
ADVAIR DISKUS	250MCG	0.35	0.33	0.38
ADVAIR DISKUS	500MCG	0.34	0.26	0.19
SYMBICORT	100MCG	0.01	0.01	0.02
SYMBICORT	200MCG	0.29	0.38	0.40

Move to AdDisk1 under LU (LU4A-LU6A)

In **LU4A – LU6A**, for users on triple therapy (dual) or dual therapy (ICS + LABA), 20% move to Advair Diskus as the preferred product, while other products are not covered. The following assumptions for the move to Advair Diskus were made:

Table 19 Assumptions for Move to AdDisk1 under LU (LU4A-LU6A)

Assumptions
Users of combination therapy remain on current combination therapy.
A proportion of users on triple therapy (dual) or dual therapy (ICS + LABA) move to combination therapy. This move is based on current ICS users (PULMICORT and FLOVENT DISKUS users, FLOVENT HFA users, and Other ICS users).
Use of combination therapy in terms of number of prescription and number of users remain the same as for ICS for ADVAIR DISKUS, and the number of units is halved.
20% reduction in cost of Advair Diskus.

The following table illustrates how users on triple therapy (dual) or dual therapy (ICS + LABA) moved to Advair Diskus.

Table 20 Details of Move to AdDisk1 under LU (LU4A-LU6A)

Details of Move to Advair Diskus			
Users on triple therapy (dual) or dual therapy (ICS + LABA), whose initial therapy is:		**Will move to:**	
PULMICORT	200MCG	ADVAIR DISKUS	based on current usage
PULMICORT	400MCG	ADVAIR DISKUS	based on current usage
PULMICORT	100MCG	ADVAIR DISKUS	based on current usage
FLOVENT DISKUS	250MCG	ADVAIR DISKUS	250MCG
FLOVENT DISKUS	500MCG	ADVAIR DISKUS	500MCG
QVAR	50MCG	ADVAIR DISKUS	based on current usage
QVAR	100MCG	ADVAIR DISKUS	based on current usage
FLOVENT HFA	50MCG	ADVAIR DISKUS	100MCG
FLOVENT HFA	125MCG	ADVAIR DISKUS	250MCG
FLOVENT HFA	250MCG	ADVAIR DISKUS	500MCG
ALVESCO	100MCG	ADVAIR DISKUS	based on current usage
ALVESCO	200MCG	ADVAIR DISKUS	based on current usage

The proportion of users moving to Advair Diskus by COPD severity was based on current usage. The following quantifies the proportion of users moving to Advair Diskus by COPD severity:

Table 21 Proportion of Users Moving to AdDisk1 under LU (LU4A-LU6A) by COPD Severity

Proportion of Users Moving to Advair Diskus by COPD Severity				
Combination therapy:		**Very Severe**	**Severe**	**Moderate**
ADVAIR DISKUS	100MCG	0.01	0.01	0.02
ADVAIR DISKUS	250MCG	0.50	0.55	0.66
ADVAIR DISKUS	500MCG	0.49	0.44	0.32

Move to Symb1 under LU (LU4S-LU6S)

In **LU4S – LU6S**, for users on triple therapy (dual) or dual therapy (ICS + LABA), 20% move to Symbicort as the preferred product, while other products are not covered. The following assumptions for the move to Symbicort were made:

Table 22 Assumptions for Move to Symb1 under LU (LU4S-LU6S)

Assumptions
Users of combination therapy remain on current combination therapy.
A proportion of users on triple therapy (dual) or dual therapy (ICS + LABA) move to combination therapy. This move is based on current ICS users (PULMICORT and FLOVENT DISKUS users, FLOVENT HFA users, and Other ICS users).
Use of combination therapy in terms of number of prescription, number of users, and number of units remain the same as for ICS for SYMBICORT.
20% reduction in cost of Symbicort.

The following table illustrates how users on triple therapy (dual) or dual therapy (ICS + LABA) moved to Symbicort.

Table 23 Details of Move to Symb1 under LU (LU4S-LU6S)

Details of Move to Symbicort			
Users on triple therapy (dual) or dual therapy (ICS + LABA), whose initial therapy is:		**Will move to:**	
PULMICORT	200MCG	SYMBICORT	100MCG
PULMICORT	400MCG	SYMBICORT	200MCG
PULMICORT	100MCG	SYMBICORT	100MCG
FLOVENT DISKUS	250MCG	SYMBICORT	based on current usage
FLOVENT DISKUS	500MCG	SYMBICORT	based on current usage
QVAR	50MCG	SYMBICORT	based on current usage
QVAR	100MCG	SYMBICORT	based on current usage
FLOVENT HFA	50MCG	SYMBICORT	based on current usage
FLOVENT HFA	125MCG	SYMBICORT	based on current usage
FLOVENT HFA	250MCG	SYMBICORT	based on current usage
ALVESCO	100MCG	SYMBICORT	based on current usage
ALVESCO	200MCG	SYMBICORT	based on current usage

The proportion of users moving to Symbicort by COPD severity was based on current usage. The following quantifies the proportion of users moving to Symbicort by COPD severity:

Table 24 Proportion of Users Moving to Symb1 under LU (LU4S-LU6S) by COPD Severity

Proportion of Users Moving to Symbicort by COPD Severity				
Combination therapy:		**Very Severe**	**Severe**	**Moderate**
SYMBICORT	100MCG	0.04	0.03	0.04
SYMBICORT	200MCG	0.96	0.97	0.96

Move to AdDisk2 under LU (LU7A-LU9A)

In **LU7A – LU9A**, for users on Alvesco and QVAR triple therapy (dual) or dual therapy (ICS + LABA), 20% move to Advair Diskus as the preferred product, while other products are available under EAP. The following assumptions for the move to combination therapy were made:

Table 25 Assumptions for Move to AdDisk2 under LU (LU7A-LU9A)

Assumptions
Users of combination therapy remain on current combination therapy.
A proportion of users on triple therapy (dual) or dual therapy (ICS + LABA) move to combination therapy. This move is based on current ICS users (PULMICORT and FLOVENT DISKUS users, FLOVENT HFA users, and Other ICS users).
Use of combination therapy in terms of number of prescription, number of users, and number of units remain the same as for ICS for SYMBICORT.
Use of combination therapy in terms of number of prescription and number of users remain the same as for ICS for ADVAIR DISKUS, and the number of units is halved.
20% reduction in cost of Advair Diskus.

The following table illustrates how users on triple therapy (dual) or dual therapy (ICS + LABA) moved to combination product (ICS+LABA).

Table 26 Details of Move to AdDisk2 under LU (LU7A-LU9A)

Details of Move to Advair Diskus			
Users on triple therapy (dual) or dual therapy (ICS + LABA), whose initial therapy is:		**Will move to:**	
PULMICORT	200MCG	SYMBICORT	100MCG
PULMICORT	400MCG	SYMBICORT	200MCG
PULMICORT	100MCG	SYMBICORT	100MCG
FLOVENT DISKUS	250MCG	ADVAIR DISKUS	250MCG
FLOVENT DISKUS	500MCG	ADVAIR DISKUS	500MCG
QVAR	50MCG	ADVAIR DISKUS	based on current usage
QVAR	100MCG	ADVAIR DISKUS	based on current usage
FLOVENT HFA	50MCG	ADVAIR DISKUS	100MCG
FLOVENT HFA	125MCG	ADVAIR DISKUS	250MCG
FLOVENT HFA	250MCG	ADVAIR DISKUS	500MCG
ALVESCO	100MCG	ADVAIR DISKUS	based on current usage
ALVESCO	200MCG	ADVAIR DISKUS	based on current usage

The proportion of users moving to combination therapy by COPD severity was based on current usage. The following quantifies the proportion of users moving to combination therapy by COPD severity:

Table 27 Proportion of Users Moving to AdDisk2 under LU (LU7A-LU9A) by COPD Severity

Proportion of Users Moving to AdDisk2 by COPD Severity				
Combination therapy:		**Very Severe**	**Severe**	**Moderate**
ADVAIR DISKUS	100MCG	0.01	0.01	0.02
ADVAIR DISKUS	250MCG	0.50	0.55	0.66
ADVAIR DISKUS	500MCG	0.49	0.44	0.32

Move to Symb2 under LU (LU7S-LU9S)

In **LU7S – LU9S**, for users on Alvesco and QVAR triple therapy (dual) or dual therapy (ICS + LABA), 20% move to Symbicort as the preferred product, while other products are available under EAP. The following assumptions for the move to combination therapy were made:

Table 28 Assumptions for Move to Symb2 under LU (LU7S-LU9S)

Assumptions for Move to Symb2 under LU
Users of combination therapy remain on current combination therapy.
A proportion of users on triple therapy (dual) or dual therapy (ICS + LABA) move to combination therapy. This move is based on current ICS users (PULMICORT and FLOVENT DISKUS users, FLOVENT HFA users, and Other ICS users).
Use of combination therapy in terms of number of prescription, number of users, and number of units remain the same as for ICS for SYMBICORT.
Use of combination therapy in terms of number of prescription and number of users remain the same as for ICS for ADVAIR DISKUS, and the number of units is halved.
20% reduction in cost of Symbicort.

The following table illustrates how users on triple therapy (dual) or dual therapy (ICS + LABA) moved to combination product (ICS+LABA).

Table 29 Details of Move to Symb2 under LU (LU7S-LU9S)

Details of Move to Advair Diskus			
Users on triple therapy (dual) or dual therapy (ICS + LABA), whose initial therapy is:		**Will move to:**	
PULMICORT	200MCG	SYMBICORT	100MCG
PULMICORT	400MCG	SYMBICORT	200MCG
PULMICORT	100MCG	SYMBICORT	100MCG
FLOVENT DISKUS	250MCG	ADVAIR DISKUS	250MCG
FLOVENT DISKUS	500MCG	ADVAIR DISKUS	500MCG
QVAR	50MCG	SYMBICORT	based on current usage
QVAR	100MCG	SYMBICORT	based on current usage
FLOVENT HFA	50MCG	SYMBICORT	based on current usage
FLOVENT HFA	125MCG	SYMBICORT	based on current usage
FLOVENT HFA	250MCG	SYMBICORT	based on current usage
ALVESCO	100MCG	SYMBICORT	based on current usage
ALVESCO	200MCG	SYMBICORT	based on current usage

The proportion of Alvesco and QVAR triple therapy (dual) or dual therapy (ICS + LABA) users moving to Symbicort by COPD severity was based on current usage. The following quantifies the proportion of users moving to combination therapy by COPD severity:

Table 30 Proportion of Users Moving to Symb2 under LU (LU7S-LU9S) by COPD Severity

Proportion of Users Moving to Symb2 by COPD Severity				
Combination therapy:		**Very Severe**	**Severe**	**Moderate**
SYMBICORT	100MCG	0.04	0.03	0.04
SYMBICORT	200MCG	0.96	0.97	0.96

Appendix C2 – Alternative Approaches to Reimbursement Results

The following tables present the forecasted expenditure and budget impact for each alternative approach to reimbursement.

Table 31 Move to Combination Product in LU (LU1-LU3) Results

COMBO MOVED TO LU:	LU1	LU2	LU3
	For Very Severe	At Least Severe	At Least Moderate
ICS	$12,432,802	$12,405,445	$12,308,201
LABA	$1,420,323	$1,395,082	$1,301,805
LAMA	$47,132,103	$47,132,103	$47,132,103
ICS+LABA*	$80,605,376	$80,648,860	$80,808,645
ADVAIR DISKUS 100MCG	$523,947	$524,025	$524,394
ADVAIR DISKUS 250MCG	$21,642,767	$21,652,827	$21,690,710
ADVAIR DISKUS 500MCG	$20,482,153	$20,504,293	$20,581,941
SYMBICORT 100MCG	$418,828	$423,745	$448,077
SYMBICORT 200MCG	$17,661,378	$17,667,666	$17,687,219
Total	$141,590,604	$141,581,490	$141,550,754
Budget Impact			
$	-$8,427	-$17,540	-$48,277
%	↓ 0.006%	↓ 0.012%	↓ 0.034%

ICS+LABA* = includes inhaled aerosol and powder form

LU1 would lead to a 0.006%reduction in COPD therapy expenditure, while LU2 and LU3 would lead to a 0.012% and 0.034% reduction respectively.

Summary of Findings for Table 31

1. Moving to LU, whereby users on triple therapy (dual) and dual therapy (ICS + LABA) move to combination therapy (ICS+LABA combination product) (LU1-LU3), would lead to a reduction in total costs ranging from COPD expenditure ranged from 0.006%-0.034% (a reduction of $8,427for users with very severe COPD to $48,277for users with at least moderate).

Table 32 Move to Advair Diskus under LU (LU4A-LU6A) Results

AdDisk1 under LU:	LU4A	LU5A	LU6A
	At Least Moderate	At Least Severe	For Very Severe
ICS	$12,308,201	$12,405,445	$12,432,802
LABA	$1,301,805	$1,395,082	$1,420,323
LAMA	$47,132,103	$47,132,103	$47,132,103
ICS+LABA*	$72,270,239	$77,079,688	$78,529,834
ADVAIR DISKUS 100MCG	$420,600	$498,300	$511,000
ADVAIR DISKUS 250MCG	$17,399,809	$20,152,790	$20,802,040
ADVAIR DISKUS 500MCG	$16,503,313	$18,482,082	$19,270,279
SYMBICORT 100MCG	$414,719	$414,719	$414,719
SYMBICORT 200MCG	$17,655,494	$17,655,494	$17,655,494
Total	$133,012,348	$138,012,318	$139,515,062
Budget Impact			
$	-$8,586,683	-$3,586,713	-$2,083,968
%	↓ 6.064%	↓ 2.533%	↓ 1.472%

ICS+LABA* = includes inhaled aerosol and powder form

LU4A would lead to a 6.064% reduction in COPD therapy expenditure, while LU5A and LU6A would lead to a 2.533% and 1.472% reduction respectively.

Table 33 Move to Symbicort under LU (LU4S-LU6S) Results

Symb1 under LU:	LU4S	LU5S	LU6S
	At Least Moderate	At Least Severe	For Very Severe
ICS	$12,308,201	$12,405,445	$12,432,802
LABA	$1,301,805	$1,395,082	$1,420,323
LAMA	$47,132,103	$47,132,103	$47,132,103
ICS+LABA*	$77,093,161	$79,278,438	$79,933,512
ADVAIR DISKUS 100MCG	$523,877	$523,877	$523,877
ADVAIR DISKUS 250MCG	$21,632,228	$21,632,228	$21,632,228
ADVAIR DISKUS 500MCG	$20,454,900	$20,454,900	$20,454,900
SYMBICORT 100MCG	$361,268	$396,698	$405,036
SYMBICORT 200MCG	$14,244,584	$16,394,431	$17,041,167
Total	$137,835,270	$140,211,068	$140,918,740
Budget Impact			
$	-$3,763,760	-$1,387,963	-$680,291
%	↓ 2.658%	↓ 0.980%	↓ 0.480%

ICS+LABA* = includes inhaled aerosol and powder form

LU4S would lead to 2.658%reduction in COPD therapy expenditure, while LU5S and LU6S would lead to a 0.980% and 0.480% reduction respectively.

Summary of Findings for Tables 32 & 33

1. Moving Advair Diskus to LU as the preferred product, while other products are not covered (LU4A-LU6A), would lead to a reduction in total costs ranging from 1.472% -6.064 (savings of $2.1 million for users with very severe COPD to $8.6 million for users with at least moderate).
2. However, moving Symbicort to LU was the preferred product, while other products are not covered (LU4S-LU6S), would lead to smaller savings between 0.7 million for users with very severe COPD to $3.8 million for users with at least moderate.

Table 34 Move to Advair Diskus under LU (LU7A-LU9A) Results

AdDisk2under LU:	LU7A	LU8A	LU9A
	At Least Moderate	At Least Severe	For Very Severe
ICS	$12,308,201	$12,405,445	$12,432,802
LABA	$1,301,805	$1,395,082	$1,420,323
LAMA	$47,132,103	$47,132,103	$47,132,103
ICS+LABA*	$72,251,571	$77,071,704	$78,524,574
ADVAIR DISKUS 100MCG	$419,794	$498,123	$510,930
ADVAIR DISKUS 250MCG	$17,364,046	$20,141,203	$20,795,309
ADVAIR DISKUS 500MCG	$16,475,338	$18,471,003	$19,264,687
SYMBICORT 100MCG	$447,524	$423,573	$418,747
SYMBICORT 200MCG	$17,668,565	$17,661,498	$17,658,596
Total	$132,993,680	$138,004,334	$139,509,802
Budget Impact			
$	-$8,605,351	-$3,594,697	-$2,089,229
%	↓ 6.077%	↓ 2.539%	↓ 1.475%

ICS+LABA* = includes inhaled aerosol and powder form

LU7A would lead to a 6.077% reduction in COPD therapy expenditure, while LU8A and LU9A would lead to a 2.539%and 1.475% reduction respectively.

Table 35 Move to Symbicort under LU (LU7S-LU9S) Results

Symb2 under LU:	LU7S	LU8S	LU9S
	At Least Moderate	At Least Severe	For Very Severe
ICS	$12,308,201	$12,405,445	$12,432,802
LABA	$1,303,155	$1,396,432	$1,421,672
LAMA	$47,132,103	$47,132,103	$47,132,103
ICS+LABA*	$77,095,901	$79,279,482	$79,934,207
ADVAIR DISKUS 100MCG	$523,877	$523,877	$523,877
ADVAIR DISKUS 250MCG	$21,637,490	$21,633,954	$21,632,935
ADVAIR DISKUS 500MCG	$20,456,644	$20,455,742	$20,455,742
SYMBICORT 100MCG	$361,146	$396,656	$405,012
SYMBICORT 200MCG	$14,240,441	$16,392,948	$17,040,336
Total	$137,839,359	$140,213,461	$140,920,784
Budget Impact			
$	-$3,759,671	-$1,385,570	-$678,246
%	↓ 2.655%	↓ 0.979%	↓ 0.479%

ICS+LABA* = includes inhaled aerosol and powder form

LU7S would lead to a 2.655%reduction in COPD therapy expenditure, while LU8S and LU9S would lead to a 0.979% and 0.479% reduction respectively.

Summary of Findings for Tables 34 & 35

1. Moving Advair Diskus to LU as the preferred product based on a 20% price reduction, while Symbicort is available under EAP (LU7A-LU9A) would lead to a reduction in total costs ranging 1.475%- 6.077% (savings of $2.1 million for users with very severe COPD to $8.6 million for users with at least moderate).
2. However, moving Symbicort to LU as the preferred product, based on a 20% price reduction, while Advair Diskus is available under EAP (LU7S-LU9S) would lead to smaller savings, between 0.7 million for users with very severe COPD to $3.8 million for users with at least moderate).