ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

FINAL REPORT

Inhaled Corticosteroids (ICS) + Long-Acting Beta-Agonists (LABA) for treatment of asthma

Pharmacoeconomics Unit

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Briefing Summary

- This report assesses the current evidence for the cost-effectiveness of ICS in combination with LABA for chronic treatment of asthma as compared to ICS alone, and analyses the economic impact of alternative changes to the funding status of asthma treatments.

- An independent Canadian study from 2009 was well-designed and may be applicable to the question at hand, though more recent clinical studies were not included the evidence base. This study concluded that a strategy of adding LABA to ICS would only be cost effective in patients who were uncontrolled on high dose ICS. For patients with poor control on lower dose ICS, increasing the dose of ICS would be more cost effective than adding a LABA.

- Analysis based on a de novo economic model found that the introduction of LABA before patients have tried high dose ICS monotherapy does not appear justified based on the criteria of cost-effectiveness.

- A policy of not funding either low dose ICS+LABA combination products or low and medium dose ICS+LABA combination products, would generate costs savings. However, if such policies lead to a reasonable proportion of patients uncontrolled on ICS moving to higher dose ICS+LABA combination products, no savings will arise.

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List of Abbreviations

$Int	International dollars
ACQ	Asthma Control Questionnaire
AQLQ	Asthma Quality of Life Questionnaire
CADTH	Canadian Agency for Drugs and Technologies in Health
CCA	cost-consequence analysis
CDN$	Canadian dollars
CEA	cost-effectiveness analysis
CIHI	Canadian Institute for Health Information
COPD	chronic obstructive pulmonary disease
CUA	cost-utility analysis
DM	German Marks
DSA	deterministic sensitivity analysis
EQ-5D	European Quality of Life-5 Dimensions
ICER	incremental cost-effectiveness ratio
ICES	Institute for Clinical Evaluative Sciences
ICS	inhaled corticosteroids
ICS + LABA	inhaled corticosteroids and long-acting beta2-agonist via separate inhalers (dual therapy)
ICS+LABA	inhaled corticosteroids in combination with long-acting beta2-agonist (combination product)
ICUR	incremental cost-utility ratio
KAS	Kelley-Anne Sabarre
KT	Kylie Tingley
LABA	long-acting $beta_2$-agonist
MCS	Monte Carlo simulation
MOHLTC	Ontario Ministry of Health and Long-Term Care
N/A	not applicable
NGL	Dutch Guilders
NHS EED	National Health Service Economic Evaluation Database
NIHR	National Institute for Health Research
OPDP	Ontario Public Drug Plan
PAQLQ	Paediatric Asthma Quality of Life Questionnaire
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
RCT	randomized controlled trial
SA	sensitivity analysis
SABA	short-acting beta-agonist
SEK	Swedish Krona
USD$	American dollars

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Executive Summary

Research Questions

RQ1. What is the current evidence for the cost-effectiveness of ICS in combination with LABA for chronic treatment of asthma compared to ICS alone?

RQ2. Based on a de novo economic model, what is the cost-effectiveness of ICS in combination with LABA for chronic treatment of asthma compared to ICS alone?

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

Review of Economic Literature

In brief, this review highlights current evidence for the cost-effectiveness of ICS in combination with LABA for chronic treatment of asthma compared to ICS alone.

There were few independent analyses assessing the cost-effectiveness of ICS in combination with LABA for chronic treatment of asthma compared to ICS alone. Most studies were either manufacturer sponsored or authors had industry affiliations; in both circumstances, study results favoured the manufacturer's therapy.

One independent Canadian study was well-designed and may be applicable to the question at hand. This study, sponsored by CADTH, was a cost-effectiveness/utility analysis of LABA in addition to ICS compared to ICS alone in adolescents and adults with asthma.[1] Patients were divided in one of three categories: steroid naïve patients, low dose ICS users, and medium dose ICS users. Within this study, the incremental cost utility ratios for ICS plus LABA compared to ICS alone ranged from $0.19 million to $3.3 million per QALY gained. Thus, a strategy of adding LABA to ICS would only be cost-effective in patients who were uncontrolled on high dose ICS. For patients with poor control on lower dose ICS, increasing the dose of ICS would be more cost effective than adding a LABA. This study did not include costs associated with adverse events, or a comparison of specific ICS+LABA and ICS therapies. In addition, as it was published in 2008, it may not be reflective of the current evidence base.

An independent UK study conducted by Lenney and associates compared the cost-effectiveness of ICS+LABA (fluticasone propionate 100 µg/salmeterol 50 µg twice a day) to ICS (fluticasone propionate 100 µg twice a day plus placebo once a day) in children with asthma aged 6-14.[2] The incremental cost-utility ratio of ICS+LABA compared to ICS alone was £12,054 per QALY gained. However, the restrictive trial population makes it difficult to generalize to a wider patient population. In addition, this study compared the same dose of ICS with and without the addition of a LABA rather than a reduced dose of ICS with LABA. The study concluded that it was not possible to determine whether adding a LABA to those receiving ICS can reduce the number of exacerbations in children with uncontrolled asthma.

Given the limitations of one of the studies and the need to incorporate more recent evidence, a de novo economic model is required to assess the cost-effectiveness of ICS+LABA compared to ICS alone using

recent data from the Canadian context.

Refer to Appendix A - A Systematic Review of Economic Evidence for a detailed report of the review of economic literature for ICS combined with LABA for asthma.

De novo Economic Evaluation

The objective of the primary economic evaluation was to assess the cost-effectiveness of alternative strategies for incorporating LABA plus ICS maintenance therapy into the management of asthma patients. Specifically, the objective was to determine at what stage the incorporation of LABA plus ICS maintenance therapy into patient management would be cost-effective.

Analysis consisted of a cost-utility analysis (CUA) conducted from the perspective of a provincial ministry of health. Effectiveness was assessed in the form of QALYs with a one year time horizon. Analysis was based on a Markov cohort model developed to predict the outcomes of each of the pharmaceutical management strategies. Four distinct strategies were considered. The strategies relate to the time point at which ICS+LABA combination products are adopted: for patients who are naïve to ICS (Strategy 1), after lack of control on low dose ICS (Strategy 2), after lack of control on moderate dose ICS (Strategy 3) and after lack of control on high dose ICS (Strategy 4).

The model used data from the companion systematic review, a previous Canadian HTA and appropriate sources for costs and utility values. Detailed deterministic and probabilistic sensitivity analyses were also conducted.

The incremental cost-utility ratio (ICUR) decreases the later a LABA is introduced into therapy for analysis at 1 year. The incremental cost per QALY gained from initiating treatment with a LABA plus ICS rather than introducing LABA after lack of control on low dose ICS monotherapy is $1.27 million. The incremental cost per QALY gained from introducing LABA after lack of control on low dose ICS monotherapy compared to introducing it after lack of control on medium dose ICS monotherapy is $410,963. Finally, the incremental cost per QALY gained from introducing LABA after lack of control on medium dose ICS monotherapy compared to introducing it after lack of control on high dose ICS monotherapy is $332,684.

For threshold values for a QALY up to $100,000 the probability that strategy 4 (adding LABA to patients uncontrolled on high dose ICS) is optimal is 100%. For all threshold values between $100,000 and $200,000, the probability that either Strategy 1 (adding LABA to treatment naïve patients), Strategy 2 (adding LABA to patients uncontrolled on low dose ICS), or Strategy 3 (adding LABA to patients uncontrolled on medium dose ICS) are optimum is never greater than 10%.

The economic analysis found that the later LABA was introduced into therapy, the more cost-effective the treatment strategy became. Thus, the optimal strategy considered was introducing LABA to patients when they were uncontrolled with high doses of ICS.

Exploratory analysis showed that if the combination of LABA and ICS were shown to be corticosteroid

sparing, and increasing doses of ICS were associated with reduced utility, earlier introduction of combination therapy in patients uncontrolled on medium dose ICS would be cost-effective. The data to support these assumptions, however, is currently lacking.

In conclusion, the introduction of LABA before patients have tried high dose ICS monotherapy does not appear justified based on the criteria of cost-effectiveness.

Budget Impact Analysis

An applied, policy oriented economic model focusing on financial impact was created to facilitate consideration of alternative reimbursement scenarios for asthma therapy. A budget impact analysis used the most recently available year of OPDP usage data (April 2012 to March 2013). Asthma patients aged 12 years and older who were dispensed at least one prescription for asthma therapy (LABA, LAMA, ICS, ICS+LABA) in Ontario were included in the analysis. The model was developed using Microsoft Excel.

The current cost of asthma products was compared to potential alternative reimbursement scenarios. The first scenario is that ICS+LABA is covered only after a trial of medium dose ICS – this precludes coverage of combination therapies including low dose ICS+LABA. The second scenario is that ICS+LABA is covered only after a trial of high dose ICS – this precludes coverage of combination therapies including low and medium dose ICS+LABA. Sensitivity analysis assessed the impact of patients being moved to higher dose ICS in combination with LABA: e.g. if combination therapies with low dose ICS+LABA are not covered, patients may be moved to a combination of medium dose ICS+LABA when uncontrolled on low dose ICS.

Total OPDP expenditure on asthma therapy (ICS, LABA, ICS+LABA and LAMA) was $112.6 million (from April 2012 to March 2013). Assuming a policy whereby combination products involving low dose ICS+LABA are not funded and assuming all patients uncontrolled on low dose ICS move to medium dose ICS would lead to a small absolute reduction in total asthma therapy expenditure (savings of $0.4 million). Smaller cost savings are expected however, if half of the patients uncontrolled on low dose ICS move to medium dose ICS+LABA (savings of $87.3 thousand).

Assuming a policy whereby combination products involving low and medium dose ICS+LABA are not funded and assuming all patients uncontrolled on low dose ICS move to medium dose ICS and patients uncontrolled on medium dose move to high dose ICS would lead to greater savings (a reduction of $4.4 million). However, if half of the patients uncontrolled on medium dose ICS move to high dose ICS+LABA costs will increase (an increase of $2.1 million).

Assuming a policy of not funding low and medium dose ICS+LABA combination products would lead to the greatest savings. However, under a scenario whereby 50% of patients uncontrolled on moderate ICS move to a high dose ICS+LABA combination product, not funding ICS+LABA combination products may lead to increased costs.

Appendices
Appendix A - A Systematic Review of Economic Evidence

Research Question

What is the current evidence for the cost-effectiveness of ICS plus LABA compared to ICS alone in the chronic management of asthma?

Review of Published Literature

Search Strategy and Findings

Search Strategy

A search of the literature from 1946 to Present (2014 June 13) in Ovid Medline (indexed, in-process and other non-indexed) and Embase Classic & Embase 1947 to 2014 June 12 was conducted in order to capture all relevant literature. Key words relating to ICS in combination with LABA for the treatment of asthma 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 packages 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 NHS EED were also 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 websites. Finally, the reference lists of relevant studies were hand searched for additional relevant articles.

Search Findings

In total 2626 citations were identified: 2595 citations from the original search, 28 additional citations from manufacturers which were different from the original search and three citations from grey literature.

Two reviewers (KAS and KT) independently reviewed the literature searches in order to identify potential articles for critical appraisal. Any disagreements were resolved through consensus.

Of the 2626 citations that were identified, a total of 198 economic citations were identified for potential inclusion within the report. 2372 citations were excluded for the following reasons: not an economic analysis, not asthma, or not relevant intervention. An additional 56 citations were excluded because the reports were non-English, not available or not full text. Results of the search can be found in Appendix A3: Results of Search.

The 198 potential studies identified during the literature review were reviewed by two reviewers (KAS and KT). Of these, 16 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

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

Summary and Critical Appraisal of Included Studies: Asthma

Included Studies

Of the sixteen reports selected for inclusion, the majority were European studies (UK, Sweden, Netherlands, Denmark, Germany, and Spain),[2-14] two were Canadian studies,[1,15] and one was an American study.[16] Fourteen studies were either sponsored by manufacturers or linked to industry.[3-16] Those two studies independent of industry sponsorship were sponsored by CADTH[1] and by NIHR Health Technology Assessment Programme.[2].

A total of nine studies were cost-effectiveness analyses,[3,4,7,9,11-14,16] four were cost-utility analyses,[2,5,6,15] two were both cost-effectiveness and cost-utility analyses,[1,8] and one was a cost-effectiveness and cost-consequence analysis[10].

Overall, the most common ICS comparator was fluticasone propionate, followed by budesonide, and then beclometasone dipropionate. Few studies examined more than one ICS comparator[5,16] or ICS products as a whole.[1,3] The most common ICS+LABA combination product was fluticasone propionate/salmeterol.

The majority of reports used a trial based analysis.[2-4,6,7,9,11-14] Of the remaining studies two used Markov models,[1,8] and four used a decision analytic model.[5,10,15,16] Time horizons considered in the analyses ranged from 12 weeks to a lifetime, with only one study considering a lifetime time frame. Many considered a 12 week time frame[1,7,8,12-14] or a one year time horizon.[3-6,9,10,15,16]

All but one study considered a health care system or third party payer perspective; three of which also considered a societal perspective.[1,15,16] The remaining study considered solely a societal perspective.[3]

A total of seven studies considered low dose ICS,[2,4,7-9,12,14] two considered medium dose ICS,[5,13] and one considered high dose ICS in their analysis.[11] One study considered separate analyses for low and medium dose ICS,[10] while two others considered separate analyses for low, medium, and high dose ICS.[1,15] The rest did not specific ICS dosage[16] or grouped low and medium dose ICS in their analysis.[3,6] A common limitation of studies was that they compared the same dose of ICS with or without LABA rather than a higher dose of ICS compared to a lower dose in combination with LABA. Thus, the relevance of such studies to the reimbursement issue may be limited.

Patient populations varied across the studies, including: adults only (≥18 years), [3,6,7,10] children and adolescents (<18 years),[2] adolescents and adults (≥12 years),[1,8,9,11-16] children, adolescents and adults (all ages),[4] and separate analyses for children and adolescents/adults.[5]

Most studies used effectiveness data from a single RCT,[2-4,6-14,17-23] although some studies did use data from more than one RCT or from a meta-analysis. [1,5,15,16]

Most studies used an intermediate outcome such as exacerbations avoided and symptom-free days to assess the cost-effectiveness of ICS+LABA compared to ICS alone.[3,4,7,9-14,16] Some studies did assess cost-effectiveness in terms of quality-adjusted life years (QALYs) gained.[1,2,5,6,8,15]

Of the six reports which considered utility values, three were derived from the Asthma Quality of Life Questionnaire score,[5,6,15] one used the Paediatric Asthma Quality of Life Questionnaire scores,[2] another used a published report,[1] and the last one assumed utility values.[8]

All except for one report conducted at least one form of sensitivity analysis. Many conducted only deterministic sensitivity analysis, [3,4,7,9-14] one considered non-parametric bootstrap method,[6] two conducted only probabilistic sensitivity analysis, [5,8] and three considered both deterministic and probabilistic sensitivity analysis.[1,15,16]

All of the reports used branded prices. Five studies considered adverse events in their analyses,[8,10-14] however, costs associated with adverse events were not always specified.

A detailed summary for each of the included studies is provided in Appendix A6: Characteristics of Reviewed Studies.

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; and the adoption of sensitivity analysis.

The applicability of each study was assessed in terms of: sponsorship, perspective, analysis based on distinct ICS dosage and asthma population, and reporting of results.

Common Issues

Canadian Content

Two relevant reports considered a Canadian perspective. One was sponsored by CADTH[1] and the other was sponsored by GlaxoSmithKline;[15] both of which assessed the cost-effectiveness of LABA in addition to ICS and ICS alone in adolescents and adults with asthma.

Sponsorship and Industry Affiliated Studies

Of the sixteen relevant reports, fourteen studies were either financed by manufacturers[3-7,15,16] or linked to industry where no sponsorship was disclosed, but authors were affiliated with industry.[8-14] These may be susceptible to the biases and limitations that have been found in manufacturer sponsored evaluations.[24]

Trial Based Analyses

A total of ten studies used trial based analyses.[2-4,6,7,9,11-14].

Surrogate Outcomes

Many reports considered intermediate outcomes such as exacerbations avoided and symptom-free days rather than final outcomes such as QALYs.[3,4,7,9-14,16] The use of intermediate outcomes does not yield meaningful results as it cannot facilitate assessment of cost-effectiveness across disease areas, thus providing little relevant information to decision makers.

Limited Sensitivity Analysis

Few studies conducted both deterministic and probabilistic sensitivity analyses.[1,15,16] Nine out of sixteen studies considered only deterministic sensitivity analysis. Canadian guidelines for economic evaluations encourages the use of probabilistic sensitivity analysis.[25]

Considerations

Distinct Asthma Populations

Some studies considered distinct asthma populations such as adolescents and adults only, adults only or children only, while others combined children, adolescent and adult populations in their analysis. Analysis using distinct asthma populations based on age is important for reimbursement decisions.

ICS dosage

Some studies considered distinct ICS dosage in their analyses such as low dose ICS only, medium dose ICS only or high dose ICS only, while others combined both low and medium ICS dosages. Analysis using distinct ICS dosage is also important for the reimbursement decisions.

Asthma Therapy Market in Canada

Currently, there are four ICS+LABA available in Canada: Advair (fluticasone + salmeterol), Symbicort (budesonide + formoterol), Zenhale (mometasone + formoterol) and BreoEllipta (fluticasone + vilanterol). Advair and Symbicort are indicated for both the management of asthma and COPD, Zenhale for the management of asthma and Breo Ellipta for the management of COPD. As well, ICS+LABA for asthma are not currently available in generic form. Therefore, the use of brand name prices in the economic analyses is justified.

Canadian Studies

Ismaila et al. (2014)

Ismaila and associates compared the cost-effectiveness of ICS+LABA (salmeterol xinafoate/ fluticasone propionate 200 µg, 500 µg, 1000 µg daily) and ICS same dose or higher dose (fluticasone propionate 200 µg, 400-500 µg, 1000 µg daily) in adolescent and adult asthma patients from a Canadian health care system perspective.[15] This analysis was sponsored by GlaxoSmithKline.

The study was conducted using a decision analytic model with a 1 year time frame. Effectiveness data were derived from a meta-analysis. Efficacy measures included symptom-free days and QALYs. Utility values were derived from the GOLD study,[26] where scores from the asthma quality of life questionnaire were mapped to EQ-5D. Costs included within the model were: cost of medication, cost of health care service (hospitalization, ER visits, outpatient visits, physician visits, home visits, telephone calls), and

cost of rescue medication. Costs associated with adverse events were not considered.

Incremental cost-utility ratios for ICS+LABA compared to same dose were $43,981 per QALY (low dose ICS), $42,911 per QALY (medium dose ICS), and $54,411 per QALY (high dose ICS). Incremental cost-utility ratios for ICS+LABA compared to increased dose were $24,959 per QALY (medium dose ICS) and $3,432 per QALY (high dose ICS). In deterministic analysis, results were sensitive to efficacy. Results were insensitive to a scenario using hospitalization costs from Ontario. At a willingness to pay of $50,000 per QALY, the probability of ICS+LABA being cost effective compared to similar dose ICS was 77% (low dose ICS), 78% (medium dose ICS), and 39% (high dose ICS). At a willingness to pay of $50,000 per QALY, the probability of ICS+LABA being cost effective compared to increased dose ICS was 86% (medium dose ICS) and 99% (high dose ICS).

This study was analyzed based on ICS dosage (low, medium, high). As well, this analysis considered a distinct asthma population (adolescents and adults) and considered final outcomes.

A limitation of this study is the assumption that the utility value was the same for a "well controlled" (WC), "not well-controlled but without exacerbation" (NWC), and "exacerbations" state. This is highly unlikely given the heterogeneity in the definition of these states.

Applicability of this study may be further limited given that it is not an independent study.

Bond et al. (2009)

A 2009 study by Bond and colleagues, sponsored by CADTH, was a cost-effectiveness/utility analysis of LABA in addition to ICS and ICS alone in adolescents and adults with asthma.[1]

The study was conducted using a Markov model with a 12-week time frame and a one week cycle length from a government perspective. Patients were divided in one of three categories: steroid naïve patients, low dose ICS users, and medium dose ICS users. Patients aged 12 and over entered the model. A total of four strategies were modelled: introduce LABA after uncontrolled asthma on high dose ICS, introduce LABA after uncontrolled asthma on medium dose ICS, introduce LABA after uncontrolled asthma on low dose ICS, and introduce LABA+ICS to steroid naïve patients. Efficacy measures included exacerbations avoided and successfully controlled weeks. Effectiveness data were derived from a meta-analysis of clinical trials. Utility values were derived from a UK National Institute for Health Research report.[27] Costs included within the model were cost of medication and cost of exacerbation management (general practitioner-management exacerbation, emergency department-managed exacerbation, and hospitalization). Costs associated with adverse events were not considered.

For steroid naïve patients, the incremental cost-effectiveness ratios of ICS plus LABA compared to ICS alone were $3.3 million per QALY, $13,385 per exacerbation avoided, and $1,375 per additional controlled weeks. For patients with asthma that is uncontrolled with low dose ICS, the incremental cost-effectiveness ratios of ICS plus LABA compared to medium dose of ICS were $1.6 million per QALY, and $6,608 per exacerbation avoided, $476 per additional controlled weeks. For patients with asthma that is uncontrolled with medium dose ICS, the incremental cost-effectiveness ratios of ICS plus LABA

compared to high dose of ICS were $0.19 million per QALY, and $787 per exacerbation avoided, and $57 per additional controlled weeks. In one-way sensitivity analysis, results were insensitive to changes to time horizon (extended to 52 weeks), utilities, cost of exacerbations, and relative risks for step up and for exacerbation. Results were also insensitive to assumptions regarding the rate of exacerbations managed through self-care, the effect of LABA-ICS on the proportion of exacerbations requiring medical management, and the probability of step down on monotherapy. Based on the probabilistic sensitivity analysis results, at a willingness to pay of $50,000 per QALY, the strategy of adding LABA to ICS only after patients are uncontrolled on high dose ICS had the highest probability of being cost effective.

Strengths of the analysis include that it is from a Canadian perspective, is independent from manufacturer sponsorship, effectiveness data were derived from a meta-analysis of clinical trials, distinct asthma population (adolescents and adults) and distinct ICS dosages were considered, final outcomes (QALY) were considered, and appropriate PSA distributions were considered. However, costs associated with adverse events were not considered and data from 2008 may not be reflective of the current evidence base.

Overall, this was a well-designed study from a Canadian perspective. However, inferences regarding specific ICS+LABA and ICS therapies cannot be made.

Non-Canadian Studies

Lenney et al. (2013)

A study by Lenney and associates was a cost-utility analysis which compared ICS+LABA (fluticasone propionate 100 µg/salmeterol 50 µg twice a day plus placebo once a day), ICS (fluticasone propionate 100 µg twice a day plus placebo once a day), and ICS + montelukast (fluticasone propionate 100 µg twice a day plus montelukast 5 mg once a day) in children and adolescents aged 6-14 with asthma.[2] Results relating to ICS + montelukast were not considered given the scope of this review. This study was sponsored by NIHR Health Technology Assessment Programme.

The study was conducted using a trial based model with a 48 week time frame. Effectiveness data were derived from a randomized controlled trial. Efficacy measures included number of asthma exacerbations requiring treatment with oral corticosteroids. Utility values were derived from Paediatric Asthma Quality of Life Questionnaire (PAQLQ) scores. Costs considered within the model were cost of medication (intervention, rescue medication, prescribed inhalers, prescribed medicines, over-the-counter medicines) and cost of health care service (GP, GP nurse, walk-in doctor, GP other, out-of-hours GP, accident and emergency visits). Costs associated with adverse events were not considered.

The incremental cost utility ratio for ICS+LABA compared to ICS was £12,054 per QALY gained. Based on non-parametric bootstrap method, the probability of ICS+LABA being cost effective compared to ICS was 60%.

This study was independent from industry sponsorship. This analysis considered low dose ICS and final outcomes (QALYs). However, the restrictive trial population makes it difficult to generalize to a wider

patient population. In addition, the study compared the same dose of ICS with and without the addition of LABA rather than reduced dose of ICS with LABA. The study concluded that it was not possible to determine whether adding a LABA to those receiving ICS can reduce the number of exacerbations in children with uncontrolled asthma. Sensitivity analyses were also limited in this study.

Applicability of this study is limited given it is not from the Canadian perspective, results are difficult to generalize due to the nature of the trial population and the study compared the same dose of ICS with and without LABA which does not relate to the reimbursement issue.

Goossens et al. (2009)

Goossens and colleagues compared the cost-effectiveness of ICS+LABA (budesonide 100 µg /formoterol 6 µg) as maintenance and reliever versus usual care. Usual care was described as commencing therapy with (low or medium daily dose of ICS (– ≤800 µg budesonide/ beclomethasone or ≤500 µg fluticasone) plus SABA if needed. However, a proportion of patients in the usual care arm (29.2%) received treatment with ICS+LABA during the trial period. This study considered a Dutch societal perspective and was sponsored by AstraZeneca.[3]

The study was conducted using a trial based model with a 1 year time frame. Patients aged 18 and over with mild to moderate asthma entered the model. Effectiveness data were derived from a randomized controlled trial. Efficacy measures were proportion of asthma-control days and Asthma Control Questionnaire (ACQ) score. Costs within the model included: cost of health care services (hospitalization, clinic visits, home visits, and telephone contact), cost of maintenance medication, and cost of production losses. Costs associated with adverse events were not considered.

Results from bootstrap replications suggest that ICS+LABA would lead to cost savings compared to usual care. Results varied by health outcome, and results were not statistically significant. Incremental cost per asthma-control days and cost per net proportion of well-controlled patients cost savings and smaller health benefits compared to ICS, while the incremental cost per improvement in ACQ score and per net proportion of improved patients for ICS+LABA would lead to cost savings and greater health benefits compared to ICS. Results were somewhat sensitive to changes in productivity losses, but insensitive to ACQ score calculation and a well-controlled asthma assumption.

Although this study considered a distinct asthma population (adults only), it had key limitations. Effectiveness data were derived from a single study and the nature of trial based studies makes it difficult to generalize the study results to other geographical settings. Final outcomes were not considered. Results were presented only in cost-effectiveness planes making it difficult to compare results across other studies. A high proportion of patients in the usual care arm (60.4%) were receiving LABA therapy immediately prior to the trial commencement so the relevance of the trial population to the reimbursement issue is limited. Furthermore, 29.2% of those in the usual care arm did receive ICS+LABA during the trial period.

Applicability of this study is limited given that it is not an independent study, it is not from the Canadian

perspective, and the trial population is not reflective of the reimbursement issue.

Wickstrøm et al. (2009)

Wickstrøm and associates compared the cost-effectiveness of ICS+LABA (budesonide 80 µg /formoterol 4.5 µg) as maintenance and reliever therapy, ICS+LABA plus SABA as needed, and ICS (budesonide 320 µg) plus SABA as needed from a Danish health care system and societal perspective.[4] Results relating to ICS+LABA as maintenance and reliever compared to ICS+LABA plus SABA as needed were not considered given the scope of this review. This analysis was financed by AstraZeneca.

The study was conducted using a trial based model with a 1 year time frame. Patients aged 4-80 years with asthma entered the model. It should be noted that 28% of patients reported LABA use at trial entry. Effectiveness data were derived from a single randomized controlled trial. Efficacy was measured as the number of severe exacerbations avoided per patient per year. Costs within the model included: cost of health care service (hospitalization, clinic visits, home visits, and ambulance), cost of medication, and cost of productivity losses. Costs associated with adverse events were not considered.

Results suggest that ICS+LABA as maintenance and reliever therapy dominated ICS plus SABA as needed. In the one-way deterministic analysis, results were insensitive to changes in costs (cost of medication, cost of hospitalization or total direct costs).

This analysis considered low ICS dosages, but had some key limitations. Effectiveness data were derived from a single study and the nature of trial based studies makes it difficult to replicate the study results and generalize to other geographical settings. Final outcomes were not considered.

Applicability of this study is limited given that it is not an independent study, it is not from the Canadian perspective, a distinct asthma population was not considered and results are difficult to generalize due to the nature of trial based studies.

Doull et al. (2007)

Doull and associates compared the cost-effectiveness of ICS+LABA (salmeterol xinafoate 100 µg/ fluticasone 200 µg, salmeterol xinafoate 100 µg/ fluticasone 500 µg, budesonide 100 µg/ formoterol 6 µg), ICS same dose or higher dose (fluticasone propionate200 µg daily, fluticasone propionate 500µg daily, beclometasone dipropionate 1000 µg daily, beclometasone dipropionate 2000 µg daily), and ICS + LABA (via separate inhalers) in asthma patients from a UK health care system perspective.[5] Results relating to ICS+LABA versus ICS+LABA or ICS+LABA compared to ICS + LABA (via separate inhalers) were not considered given the scope of this review. This analysis was sponsored by GlaxoSmithKline.

The study was conducted using a decision analytic model with a 1 year time frame. Two patient populations were considered: patients aged 12 and over and patients less than 12 years of age. Effectiveness data were derived from a meta-analysis. Symptom-free days were used as a measure of efficacy. The model assumed no differential treatment effect on mortality. Utility values were derived from the GOLD study,[26] where scores from the asthma quality of life questionnaire were mapped to EQ-5D. Costs within the model included: cost of primary care (physician home visits, survey visits,

telephone calls), cost of secondary care (emergency department visits, length of stay in intensive care, inpatient days, and outpatient visits), and cost of rescue medication. Costs associated with adverse events were not considered.

For patients aged 12 and over, the incremental cost utility ratio for ICS+LABA (salmeterol/fluticasone propionate) via Accuhaler compared to low dose ICS (fluticasone propionate) was £6,852 per QALY and via Evohaler, ICS+LABA dominated ICS. The incremental cost utility ratio for ICS+LABA (salmeterol/fluticasone propionate) compared to low dose ICS (beclometasone dipropionate) was £15,997 per QALY via Accuhaler and £5,679 per QALY via Evohaler. Results were similar for medium dose ICS; ICS+LABA dominated ICS (fluticasone propionate) and the incremental cost utility ratio for ICS+LABA compared to medium dose ICS (beclometasone dipropionate) was £14,567 per QALY. For patients under 12 years of age, the incremental cost utility ratio for ICS+LABA compared to low dose ICS (fluticasone propionate) was £63,736 per QALY via Accuhaler; and £15,739 per QALY via Evohaler. At a willingness to pay of £20,000 per QALY, the probability of ICS+LABA via Evohaler being cost effective compared to low dose ICS (fluticasone propionate) in patients aged 12 and over was 0.90; compared to medium dose ICS, the probability was 1.00; and compared to low dose in children under 12, the probability was 0.03.

This study was analyzed based on ICS dosage (low and medium) and type of ICS (fluticasone propionate, beclometasone dipropionate). As well, this analysis considered two distinct asthma populations (children and adolescents/adults) and final outcomes. However, deterministic sensitivity analysis was not performed. In addition, it was assumed that the utility value was the same for a "well controlled" (WC), "not well-controlled but without exacerbation" (NWC), and "exacerbations" state. This is highly unlikely given the heterogeneity in the definition of these states. Finally, analysis compared patients receiving the same dose ICS with or without LABA which does not relate to the reimbursement issue.

Applicability of this study may be limited given that it is not an independent study, it is not from the Canadian perspective, there are concerns over the utility values used within the analysis and comparators did not relate to the reimbursement issue.

Shih et al. (2007)

Shih and associates compared the cost-effectiveness of ICS+LABA (salmeterol 50 µg/fluticasone propionate 100 µg), ICS (fluticasone propionate), ICS (non-fluticasone propionate) and leukotriene modifiers as first-line therapy in patients with mild to moderate asthma from a US payer in managed care organization perspective.[16] Results relating to leukotriene modifiers were not considered given the scope of this review. This analysis was sponsored by GlaxoSmithKline.

The study was conducted using a decision-analysis model with a 1 year time frame. Patients (aged 12 and over) begin with initial therapy either ICS+LABA, ICS (fluticasone propionate), ICS (non-fluticasone propionate) or leukotriene modifiers and at the 3 month intervals may switch therapies (using a step-down approach). Effectiveness data were derived from randomized controlled trials with 12 week time frames and were extrapolated to a 1 year time frame. Efficacy inputs considered were symptom free

days and rescue medication free days. Treatment effect was adjusted to the rate of treatment adherence. Costs included within the model were: cost of asthma medication, emergency department visits, hospitalizations, and physician visits. Costs associated with adverse events were not considered.

The incremental cost-effectiveness ratios for ICS+LABA compared to ICS (fluticasone propionate) as first-line therapy were slightly higher at $9.55 per symptom-free day and $8.93 per rescue medication-free day. The incremental cost-effectiveness ratios for ICS+LABA compared to ICS (non-fluticasone propionate) were not presented. In one-way deterministic analysis, results were insensitive to changes to adherence and to adherence-effectiveness assumptions. Based on probabilistic sensitivity analysis results, at a willingness to pay of $14.80 per symptom-free day, ICS+LABA has 98% probability of being cost effective compared to ICS (fluticasone propionate).

Although a distinct asthma population was considered (adolescents and adults), this analysis had many limitations. The major weakness of this study related to the modeling of effectiveness; treatment effects were derived from a meta-analysis which incorporated different treatment dosages as one therapeutic option. Also, final outcomes (QALYs) were not considered.

Applicability of this study is limited given that it is not an independent study, it is not from the Canadian perspective, assumptions relating to effectiveness were not appropriate and the study results were difficult to interpret due to the outcome measures adopted.

Briggs et al. (2006)

A study by Briggs and associates, sponsored by GlaxoSmithKline, was a cost utility analysis of ICS plus LABA (salmeterol ≤50 µg /fluticasone propionate ≤500 µg twice a day) and ICS (fluticasone propionate ≤500 µg twice a day) from a UK National Health Service perspective.[6]

This trial based analysis used a one year time frame to model patients with uncontrolled asthma between the ages of 12 and 80. Patients were stratified in one of three categories: previously ICS-free patients [Stratum 1], low dose ICS users [Stratum 2], and moderate dose ICS users [Stratum 3]. The model had a dose-escalation phase [Phase 1] (using a step up approach), where patients may increase therapy dose if total control was not achieved within 7 weeks. Patients then enter a maintenance phase [Phase2], where patients remained on the same dose at the end of Phase 1. Effectiveness data were derived from a randomized controlled trial and efficacy was measured in successfully controlled weeks. Utility values were derived from AQLQ and mapped to utility scores. Costs included within the model were: cost of medication and cost of primary and secondary care visits (general practitioner home visits, primary care clinic visits, emergency department visits, and outpatient visits).

The incremental cost utility ratios for ICS+LABA versus ICS were £13,700 per QALY for patients previously ICS-free, £11,000 per QALY for low dose ICS users, and £7,600 per QALY for moderate dose ICS users. Results from non-parametric bootstrapping methods revealed a lower 95% limit of £11,000 per QALY and the upper 95% limit of £18,300 per QALY for Stratum 1; a lower 95% limit of £8,600 per QALY and the upper 95% limit of £14,600 per QALY for Stratum 2; and a lower 95% limit of £4,800 per

QALY and the upper 95% limit of £10,700 per QALY for Stratum 3.

Although this study considered stratified analysis based on ICS dosage prior to screening for study entry and considered a distinct asthma population (adolescents and adults), its major limitations are that effectiveness data were derived from a single study and that the nature of trial based studies makes it difficult to generalize the study results to other geographical settings. Finally, analysis compared patients receiving the same dose ICS with or without LABA which does not relate to the reimbursement issue.

Applicability of of this study is limited given that it is not an independent study, it is not from the Canadian perspective, results are difficult to generalize due to the nature of trial based studies and comparators did not relate to the reimbursement issue.

Ericsson et al. (2006)

Ericsson and colleagues compared the cost-effectiveness of ICS+LABA (budesonide 4.5 µg/ formoterol 160 µg and ICS (fluticasone propionate 250 µg) in asthma patients from a German and Dutch health care payer, societal, and drug plan perspective.[7] This analysis was sponsored by AstraZeneca.

The study was conducted using a trial based model with a 12 week time frame. Patients aged 18 and above with moderate asthma receiving ICS entered the model. Effectiveness data were derived from a randomized controlled trial. Efficacy was measured in number of episode-free days. Utility values were not considered. Costs within the model included: cost of medication (study, rescue and other asthma medication), cost of health care services (hospitalization, emergency room, physician and nurse visits, phone and house calls, and pharmacy contacts), and productivity costs (for societal perspective).

From a health care payer perspective, the average cost per patient was less for ICS+LABA compared to ICS (€131 compared to €210 using German costs and €101 versus €103 using Dutch costs). Similar results were found using a societal perspective and drug plan perspective. Based on the non-parametric bootstrap analysis, results were insensitive to the exclusion of Israeli data.

Although this study considered a distinct asthma population (adults only); and considered low ICS dosage, it had key limitations. The nature of trial based studies makes it difficult to replicate the study results and to generalize results to other geographical settings. Final outcomes were not considered and sensitivity analysis was limited.

Applicability of this study is limited given that it is not an independent study, it is not from the Canadian perspective, and results are difficult to interpret due to the outcome measures adopted.

Jönsson et al. (2004)

A study by Jönsson and colleagues was a cost-effectiveness analysis of ICS plus LABA (budesonide 100 µg/ formoterol 4.5 µg; budesonide 200 µg/formoterol 4.5 µg) and ICS (budesonide 100 µg; budesonide 200 µg) from both a Swedish health care payer and societal perspective.[9] Although sponsorship was not disclosed, an author was affiliated with AstraZeneca.

This trial based analysis used a one year time frame to model patients aged 12 and above with mild to moderate asthma. Effectiveness data were derived from a randomized controlled trial. Efficacy measures included the number of symptom-free days and the number of severe exacerbations per patient. Costs included within the model were: cost of medications (study, reliever, and other medication), cost of health care services (physician and nurse visits, phone calls by physician or nurse, hospital admissions, and pharmacy contacts), and absence from work (for societal perspective).

Base case results suggest ICS+LABA combinations were more effective, but more costly than ICS therapy alone. The incremental cost-effectiveness ratio of budesonide 200 µg plus formoterol 4.5 µg versus budesonide 200 µg was SEK 21 per symptom-free day. The incremental cost-effectiveness ratios for ICS+LABA (budesonide 200 µg/formoterol 4.5 µg) compared to ICS (budesonide 100 µg) were not reported. In deterministic sensitivity analysis, results were insensitive to scenarios using unit costs from the UK and Spain.

This report considered low dose ICS and distinct asthma patient populations (adolescents and adults); however, it had key limitations. 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 results to other geographical settings. Final outcomes (QALYs) were not considered and the analysis compared patients receiving the same dose ICS with or without LABA, which does not relate to the reimbursement issue.

Applicability of this study is limited given that it is not from the Canadian perspective, and results are difficult to interpret due to the outcome measures adopted and comparators did not relate to the reimbursement issue.

Price and Briggs (2002)

Price and Briggs compared the cost-effectiveness of ICS+LABA (salmeterol 50 µg/fluticasone propionate 100 µg) and ICS (fluticasone propionate 100 µg) from a UK health care system perspective.[8] This analysis was sponsored by GlaxoSmithKline.

The study was conducted using a Markov model with a 12 week time frame and a one week cycle length. Patients aged 12-70 with asthma and a FEV_1 of 40% to 85% entered the model. Efficacy inputs included proportion of successfully controlled weeks. Effectiveness data were derived from a single randomized controlled trial. In a secondary analysis, the authors assumed utility values for health states based on both a published utilities study could be interpolated for certain health states (hospital managed exacerbation, primary care–managed exacerbation, and suboptimal control health state) whilst a utility value for total control of 0.99 was assumed. Withdrawal due to adverse events (adverse events not specified) was accounted for within the model. Costs within the model were cost of medication (study, rescue, and emergency asthma), cost of hospital inpatient and emergency room care, and cost of physician consultation.

The incremental cost-effectiveness ratio for ICS+LABA compared to ICS was £20.83 per successfully

controlled week. At a willingness to pay of £45 per successfully controlled week, ICS+LABA has the greatest probability of being cost effective. In the secondary analysis, the incremental cost utility ratio for ICS+LABA compared to ICS was £1357 per QALY. Probabilistic sensitivity analysis for incremental cost per QALY ratio was not performed.

This report considered low dose ICS and distinct asthma patient populations (adolescents and adults). However, it had key limitations: effectiveness data were derived from a single RCT; deterministic sensitivity analysis was not considered and probabilistic sensitivity analysis only considered uncertainty around transition probabilities and costs. Primary analysis employed a measure of effectiveness which was not a final outcome. A secondary cost utility analysis used utility values which were not related to the states within the model and the utility value for well controlled was based on expert option and clearly biased results. Finally, analysis compared patients receiving the same dose ICS with or without LABA which does not relate to the reimbursement issue.

Applicability of this study is limited given that it is not an independent study and is not from the Canadian perspective, the results of the primary analysis are difficult to interpret due to the outcome measures adopted, the utility values employed in the secondary analysis biased results and the comparators did not relate to the reimbursement issue.

Andersson et al. (2001)

A study by Andersson and colleagues was a cost-consequence and cost-effectiveness analysis comparing ICS+LABA (budesonide 200 µg + formoterol 24 µg; budesonide 800 µg + formoterol 24 µg) to ICS (budesonide 200 µg; budesonide 800 µg) in patients with moderate asthma.[10] The analysis was sponsored by AstraZeneca and considered a health care system and societal perspective from the UK, Sweden and Spain.

This decision analytic based analysis used a one year time frame to model patients aged 18-70 years. Effectiveness data were derived from a randomized controlled trial. Efficacy measures included exacerbation, episode-free days and symptom-free days. Expert opinion was used to obtain information on mild and severe exacerbation health care service utilization data. Costs included within the model were direct medical costs (drugs, physician visits, emergency visits, and hospital stay) and indirect costs (productivity loss for societal perspective).

In the UK, direct costs associated with ICS+LABA were greater than ICS alone. In contrary, direct costs associated with were ICS +LABA less than ICS alone in Sweden. In Spain, direct costs associated with ICS+LABA (budesonide 200 µg + formoterol 24 µg) were less than ICS alone (budesonide 200 µg) and directs associated with ICS+LABA (budesonide 800 µg + formoterol 24 µg) were greater than ICS alone (budesonide 800 µg). Overall, there was a gain from adding LABA to ICS in terms of number of mild exacerbations, severe exacerbations, symptom-free days, and episode-free.

In the UK, the incremental cost-effectiveness ratio for ICS+LABA (budesonide 200 µg + formoterol 24 µg) versus ICS (budesonide 200 µg) was €4.67 per symptom-free day and €6.60 per symptom-free day for

ICS+LABA (budesonide 800 µg + formoterol 24 µg) versus ICS (budesonide 800 µg). In Sweden, ICS+LABAs dominated ICSs. In Spain, the incremental cost-effectiveness ratio for ICS+LABA (budesonide 200 µg + formoterol 24 µg) dominated ICS (budesonide 200 µg), while the incremental cost effective ratio for ICS+LABA (budesonide 800 µg + formoterol 24 µg) versus ICS (budesonide 800 µg) was €2.51 per symptom-free day.

Although this study considered a distinct asthma population (adults only) and considered distinct ICS dosages (low, medium), it had several key limitations. Effectiveness data were derived from a single study, final outcomes (QALYs) were not considered and analysis compared patients receiving the same dose ICS with or without LABA which does not relate to the reimbursement issue.

Applicability of of this study may be limited given that it is not an independent study, it is not from the Canadian perspective, results are difficult to interpret due to the outcome measures adopted and comparators do not relate to the reimbursement issue under consideration.

Lundbäck et al. (2000)

A study by Lundbäck and associates was a cost-effectiveness analysis of ICS+LABA (salmeterol 50 µg/ fluticasone propionate 250 µg) and ICS (budesonide 800 µg) from a Swedish health care system perspective.[11] Although funding source was not disclosed; authors were affiliated with GlaxoSmithKline (formerly known as Glaxo Wellcome).

This trial based analysis used a 24 week time frame to model adolescents and adults aged 12 and above with moderate to severe asthma. Effectiveness data were derived from a randomized controlled trial. Efficacy measures included successfully treated weeks, episode-free days, and symptom-free days. Costs included within the model were cost of medication (study drugs, rescue medication, other asthma-related prescription medication), cost of general practitioner contacts (home, office/practice visits, telephone calls), and cost of hospital contacts (emergency room and outpatient clinic visits, intensive care unit and inpatient days).

The incremental cost-effectiveness ratios for ICS+LABA versus ICS were SEK 31.6 per successfully treated week, SEK 51.1 per episode-free day, and SEK 9.2 per symptom-free day. In one-way deterministic analysis, results were insensitive to improvement in morning peak expiratory flow. In the best and worst case scenarios, results continued to favour ICS+LABA.

This study considered high ICS dosage and a distinct asthma population (adolescents and adults). However, it had many limitations. 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. Final outcomes such as QALY were not considered. Although deterministic sensitivity analysis was conducted, probabilistic sensitivity analysis was not considered.

Applicability of this study is limited given that it is not from the Canadian perspective and results are difficult to interpret due to the outcome measures adopted.

Palmqvist et al. (1999)

A study by Palmqvist and colleagues was a cost-effectiveness analysis of ICS plus LABA (fluticasone propionate 250 µg/ salmeterol 50 µg) and ICS (fluticasone propionate 250 µg) from a Swedish health care system perspective.[12] Although funding was not disclosed; authors were affiliated with GlaxoSmithKline (formerly known as Glaxo Wellcome).

This trial based analysis used a 12 week time frame to model adolescents and adults with moderate to severe asthma. Effectiveness data were derived from a randomized controlled trial. Efficacy measures included the mean proportion of successfully treated week, mean proportion of symptom-free days, and mean proportion of episode-free days. Costs included within the model were cost of medication (study drug, relief medication, concurrent drugs), cost of hospital contacts (emergency room visits, inpatient days), and cost of general practitioner contacts (clinic visits).

The incremental cost-effectiveness ratios for ICS+LABA versus ICS were SEK 12.6 per successfully treated week, SEK 3.9 per episode-free day, and SEK 3.9 per symptom-free day. In one way deterministic analysis, results were insensitive to changes to improvements in morning peak expiratory flow. In best and worst case scenarios, results continued to favour ICS+LABA.

This analysis considered low dose ICS and a distinct asthma population (adolescents and adults), however, it had key limitations. 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. Final outcomes such as QALY were not considered. Analysis compared patients receiving the same dose ICS with or without LABA which does not relate to the reimbursement issue.

Applicability of this study is limited given that it is not from the Canadian perspective, results are difficult to interpret due to the outcome measures adopted and results do not relate to the reimbursement issue under consideration.

Pieters et al. (1999)

A study by Pieters and associates was a cost-effectiveness analysis of ICS plus LABA (fluticasone propionate 500 µg/ salmeterol 50 µg) and ICS (fluticasone propionate 500 µg) from a Swedish health care system perspective.[13] Sponsorship was not disclosed, however, authors were affiliated with GlaxoSmithKline (formerly known as Glaxo Wellcome).

This trial based analysis used a 12 week time frame to model adolescent and adult patients with corticosteroid-dependent asthma. Effectiveness data were derived from a randomized controlled trial. Efficacy measures included the mean proportion of successfully treated week, mean proportion of symptom-free days, and mean proportion of episode-free days. Costs included within the model were cost of medication (study drug, relief medication, concurrent drugs), cost of hospital contacts (emergency room visits, inpatient days), and cost of general practitioner contacts (clinic visits).

The incremental cost-effectiveness ratios for ICS+LABA versus ICS were SEK 192.1 per successfully treated week, SEK 66.8 per episode-free day, and SEK 120.0 per symptom-free day. In one way

deterministic analysis, results were insensitive to changes to improvements in morning peak expiratory flow. In best and worst case scenarios, results continued to favour ICS+LABA.

The study had key limitations. 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. Final outcomes such as QALY were not considered. Analysis compared patients receiving the same dose ICS with or without LABA which does not relate to the reimbursement issue.

Applicability of this study is limited given that it is not from the Canadian perspective, results are difficult to interpret due to the outcome measures adopted and results do not relate to the reimbursement issue under consideration.

Johansson et al. (1999)

Johansson and colleagues compared the cost-effectiveness of ICS+LABA (salmeterol 50 µg / fluticasone propionate 100 µg) and ICS (fluticasone propionate 100 µg) from a Swedish health care system perspective.[14] Sponsorship was not disclosed; however, authors were affiliated with GlaxoSmithKline (formerly known as Glaxo Wellcome).

This trial based analysis used a 12 week time frame to model adolescents and adults aged 12 and above with asthma. Effectiveness data were derived from a randomized controlled trial. Efficacy measures included the mean proportion of successfully treated week, mean proportion of symptom-free days, and mean proportion of episode-free days. Costs included within the model were cost of medication (study drug, relief medication, concurrent drugs), cost of hospital contacts (emergency room visits, inpatient days), and cost of general practitioner contacts (clinic visits).

The incremental cost-effectiveness ratios for ICS+LABA versus ICS were 133.4 SEK per successfully treated week, 44.5 SEK per symptom-free days, and 46.9 SEK per episode-free days. In best and worst case scenarios, results continued to favour ICS+LABA. In one-way deterministic analysis, results were insensitive to changes in improvements in morning peak expiratory flow.

This analysis considered low ICS dosage and a distinct asthma population (adolescents and adults) was considered. However, it had key limitations. 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. Final outcomes (QALYs) were not considered. Analysis compared patients receiving the same dose ICS with or without LABA which does not relate to the reimbursement issue.

Applicability of this study is limited given that it is not from the Canadian perspective, results are difficult to interpret due to the outcome measures adopted and results do not relate to the reimbursement issue under consideration.

Overall Conclusions

Overall, the majority of studies identified in this review are of limited applicability to the current

Canadian setting. Most were industry sponsored or linked to industry. Only two Canadian studies were identified.[1,15] One was sponsored by CADTH[1] and the other by GlaxoSmithKline.[15]

The report sponsored by CADTH explored the cost-effectiveness of adding LABA to ICS both for ICS naïve adolescents and adults with asthma and for those experiencing poor control on ICS.[1] Results suggest that ICS plus LABA is not cost-effective for patients who are ICS naïve or who have poor control with low or moderate dose ICS compared to ICS alone. Overall, the study was well-designed from a Canadian perspective and independent of industry sponsorship. However, given analysis was conducted in 2008, results may not be reflective of the current evidence base.

The report sponsored by GlaxoSmithKline was a cost-effectiveness of ICS+LABA and ICS same dose or higher dose in adolescent and adult patients from a Canadian health care system perspective.[15] Incremental cost-utility ratios for ICS+LABA compared to same dose were $43,981 per QALY (low dose ICS), $42,911 per QALY (medium dose ICS), and $54,411 per QALY (high dose ICS). Incremental cost-utility ratios for ICS+LABA compared to increased dose were $24,959 per QALY (medium dose ICS) and $3,432 per QALY (high dose ICS). This study was analyzed based on ICS dosage (low, medium, high). As well, this analysis considered a distinct asthma population (adolescents and adults) and considered final outcomes. Applicability of this study may be limited given that it is not an independent study and there are concerns over the utility values adopted.

Of the non-Canadian studies, nine were cost-effectiveness analyses,[3,4,7,9,11-14,16] three were cost-utility analyses,[2,5,6] one was both cost-effectiveness and cost-utility analyses,[8] and another was a cost-effectiveness and cost-consequence analysis,[10].

The study conducted by Lenney et al.[2] was independent of industry sponsorship or affiliations. It compared the cost-effectiveness of ICS+LABA (fluticasone propionate 100 µg/salmeterol 50 µg twice a day) to ICS (fluticasone propionate 100 µg twice a day plus placebo once a day) in children aged 6-14 with asthma.[2] The study was a trial based analysis. The incremental cost-utility ratio of ICS+LABA compared to ICS alone was £12,054 per QALY. However, the nature of trial based studies makes it difficult to generalize the results to other geographical settings and analysis compared the same dose of ICS with and without LABA.

Results from studies affiliated by manufacturers of salmeterol/fluticasone propionate concluded that ICS+LABA was cost effective compared to ICS alone. Similarly, results from studies affiliated by manufacturers of budesonide/formoterol reported that ICS+LABA was cost effective compared to ICS alone. However, a frequent limitation was analysis compared patients receiving the same dose ICS with or without LABA which does not relate to the reimbursement issue.

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.

Relation to COPD Reports and Overall Summary

As stated previously, some ICS+LABA combination products are indicated for both COPD and asthma treatment. ODPRN has conducted three drug class reviews in the area:

ICS+LABA for chronic treatment of COPD

In April 2014, ODPRN examined the 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. A systematic review of economic evidence was conducted; a total of nine relevant reports addressed the objective of that review.

All but two were financed by manufacturers. Of the reports that were independent from industry sponsorships, one was the NCGC report,[22] and the other was a study by Oba which evaluated the cost-effectiveness of ICS+LABA compared to monotherapies (LABA or ICS) and placebo.[28] The NCGC report reached divergent conclusions depending on the source of effectiveness data which limits its usefulness in decision making,[22] while the study by Oba only used effectiveness data derived from a single randomized controlled trial and lacked transparency in reporting.[28]

Results from all manufacturer sponsored economic analyses favoured the manufacturer's treatment.

Given both contradictory results and the consistent concerns over the quality and the relevance of the available studies, it was not possible to make any inferences on which patient population the use of ICS+LABA was cost effective. As a result, ODPRN developed an independent de novo economic model to address the cost-effectiveness of ICS, LABA and LAMA as single and combination therapies.

LAMA for chronic treatment of COPD

In August 2014, ODPRN examined the current economic evidence for the cost-effectiveness of LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS for chronic treatment of COPD. A systematic review of economic evidence was conducted. A total of fourteen analyses were identified; only one included Canadian data. Most were financed by industry. More than half considered distinct COPD severity populations in the main analysis or in the sensitivity analysis. Most were a comparison of monotherapies. More than half used effectiveness data from more than one randomized controlled trial.

Results from studies sponsored by manufacturers of LAMA concluded that LAMA was cost effective compared to LABA or dominated LABA,[20,23,29-34] while results from studies sponsored by manufacturers of LABA reported the opposite.[35-37]

The results of the NCGC report varied depending on the source of effectiveness data which limits its usefulness in decision making.[38] Oba and Naik et al evaluated the cost-effectiveness of monotherapies (LAMA, LABA) compared to placebo/no therapy; ratios comparing active treatment were not presented and therefore could not be inferred.[21,39] Results from all manufacturer sponsored economic analyses favoured the manufacturer's treatment.

Similar to the ICS+LABA for COPD report, results were contradictory and there are consistent concerns over the quality of the relevance of the available studies. Subsequently, it was not possible to make any inferences over the cost-effectiveness of LAMA alone or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS. As a result, ODPRN adapted the existing de novo economic model to address the cost-effectiveness of LAMA as single or in combination with LABA and/or ICS compared to single or combination therapies incorporating LABA and ICS.

ICS+LABA for Asthma

Applicability of non-Canadian studies to any decision regarding the cost-effectiveness of ICS+LABA in asthma is limited given they are not from the Canadian perspective; all except for one was industry affiliated and favour the manufacturer's therapy.

One Canadian study independent of industry sponsorship identified was well-designed. The report concluded that ICS+LABA was not cost effective in patients who were steroid naïve or had had experienced poor control with low or medium dose ICS.

Conclusions

In brief, this review highlights current evidence for the cost-effectiveness of ICS in combination with LABA for chronic treatment of asthma compared to ICS alone.

Economic evidence for the cost-effectiveness of ICS in combination with LABA for chronic treatment of asthma compared to ICS alone suggests that there are few independent analyses; most studies have industry affiliations and favour the manufacturer's therapy.

One independent Canadian study was included. The incremental cost utility ratios for ICS plus LABA compared to ICS alone ranged from $0.19 million to $3.3 million per QALY. Thus, the study suggests that ICS+LABA is not cost effective in patients who were steroid naïve or had had experienced poor control with low or medium dose ICS. Thus LABA+ICS may be best reserved for patients who cannot achieve adequate control after a trial of high dose ICS.

Given that this analysis was conducted in 2008 and results may not be reflective of the current clinical evidence base, a de novo economic model is required to assess the cost-effectiveness of ICS+LABA compared to ICS alone using recent data from the Canadian context.

Appendix A - Appendices

Appendix A1: Search Strategy

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

Embase Classic+Embase 1947 to 2014 June 12, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present (2014 June 13)

1. exp Asthma/

2. asthma.ti,ab.

3. 1 or 2

4. Formoterol*.tw,rn.

5. (BD 40A or HSDB 7287 or Oxis or UNII-5ZZ84GCW8B).tw.

6. (eformoterol or Foradil).tw.

7. 73573-87-2.rn.

8. Indacaterol.tw,rn.

9. (Arcapta or Onbrez or QAB 149 or QAB149 or UNII-8OR09251MQ).tw.

10. 312753-06-3.rn.

11. Salmeterol*.tw,rn.

12. (Aeromax or Astmerole or "GR 33343 X" or "GR 33343X" or HSDB 7315 or SN408D or UNII-2I4BC502BT).tw.

13. 89365-50-4.rn.

14. Salmeterolxinafoate.tw,rn.

15. (Arial or Asmerole or Beglan or Betamican or Dilamax or Inaspir or Salmetedur or Serevent or Ultrabeta or UNII-6EW8Q962A5).tw.

16. 94749-08-3.rn.

17. ((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.

18. ((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.

19. ((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.

20. ((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.

21. ((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.

22. ((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.

23. (LABA or LABAs or Ultra-LABA* or UltraLABA*).tw.

24. ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and bronchodilator*).tw.

25. ((longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting) and (betamimetic* or beta-mimetic*)).tw.

26. exp Adrenergic beta-Agonists/ or Bronchodilator Agents/

27. (longacting or long-acting or ultra-longacting or ultra-long-acting or ultralongacting or ultralong-acting).tw.

28. 26 and 27

29. or/17-25,28

30. Administration, Inhalation/

31. exp Aerosols/

32. (inhal* or aerosol*).tw.

33. or/30-32

34. 29 and 33

35. or/4-16,34

36. Beclomethasone/

37. (Aerobec or AeroBec Forte or Aldecin or Apo-Beclomethasone or Ascocortonyl or AsmabecClickhaler).tw.

38. (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.

39. (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.

40. (BMJ 5800 or EINECS 224-585-9 or UNII-KGZ1SLC28Z).tw.

41. 4419-39-0.rn.

42. Budesonide/

43. (Budesonide or Micronyl or Preferid or Pulmicort or Respules or Rhinocort or "S 1320" or Spirocort or Uceris or UNII-Q3OKS62Q6X).tw.

44. 51333-22-3.rn.

45. Fluticasone.tw,rn.

46. (Cutivate or Flixonase or Flixotide or Flonase or Flovent or Fluticason* or HSDB 7740 or UNII-CUT2W21N7U).tw.

47. Glucocorticoids/

48. glucocorticoid*.tw.

49. Adrenal Cortex Hormones/

50. (corticoid* or corticosteroid* or cortico-steroid*).tw.

51. ((adrenal cortex or adrenal cortical) adj3 hormon*).tw.

52. ((adrenal cortex or adrenal cortical) adj3 steroid*).tw.

53. or/47-52

54. 33 and 53

55. or/36-46,54

56. (Fluticasone adj3 salmeterol).tw,rn.

57. (Adoair or Advair or Foxair or "Quikhale SF" or Seretide or Viani).tw.

58. (formoterol adj3 mometasone).tw,rn.

59. (Zenhale or Dulera).tw.

60. (formoterol adj3 budesonide).tw,rn.

61. (Rilast or Symbicord or Symbicort or Vannair).tw.

62. (vilanterol adj3 fluticasone).tw,rn.

63. Breo Ellipta.tw.

64. or/56-63

65. 35 or 55 or 64

66. 3 and 65

Appendix A2: List of Citations Included by Manufacturer

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

Study Reference	Additional Citation From Original Search	Relevant Citation	Reason For Inclusion/Exclusion
Halpin DM. Symbicort: a pharmacoeconomic review. J Med Econ 2008; 11(2):345-62.	No	No	Not economic evaluation
Johansson G, Andreasson EB, Larsson PE, Vogelmeier CF. Cost-effectiveness of budesonide/formoterol for maintenance and reliever therapy vs. salmeterol/fluticasone plus salbutamol in the treatment of asthma. Pharmacoeconomics 2006; 24(7): 695-708.	No	No	Not relevant intervention
Price D, Wirén A, Kuna P. Cost-effectiveness of budesonide/formoterol for maintenance and reliever asthma therapy. Allergy 2007; 62(10):1189-1198.	No	No	Not relevant intervention
Wickstrøm J, Dam N, Malmberg I, et al. Cost-effectiveness of budesonide/formoterol for maintenance and reliever asthma therapy in Denmark -- cost-effectiveness analysis based on five randomised controlled trials. Clin Respir J 2009; 3(3):169-80.	No	Yes	Selected for inclusion in this review.
Miller E, Sears MR, McIvor A, Liovas A. Canadian economic evaluation of budesonide-formoterol as maintenance and reliever treatment in patients with moderate to severe asthma. Can Respir J 2007; 14(5): 269-275.	No	No	Not relevant intervention
Miller E, FitzGerald JM. Budesonide/formoterol as maintenance and reliever treatment compared to fixed dose combination strategies - a Canadian economic evaluation. Can J Clin Pharmacol 2008; 15(2):e165-176.	No	No	Not relevant intervention
Goossens LM, Riemersma RA, Postma DS, et al. An economic evaluation of budesonide/formoterol for maintenance and reliever treatment in asthma in general practice. Adv Ther 2009; 26(9):872-85.	No	Yes	Selected for inclusion in this review.

Study Reference	Additional Citation From Original Search	Relevant Citation	Reason For Inclusion/Exclusion
Lundborg M, Wille S, Bjermer L, et al. Maintenance plus reliever budesonide/formoterol compared with a higher maintenance dose of budesonide/formoterol plus formoterol as reliever in asthma: an efficacy and cost-effectiveness study. Curr Med Res Opin 2006; 22(5): 809-821.	No	No	Not relevant intervention
Tamminen K, Laine J, Soini E, et al. Cost-effectiveness analysis of budesonide/formoterol maintenance and reliever therapy vs. fixed combination treatments for asthma in Finland. Curr Med Res Opin 2008; 24(12):3453-3461.	No	No	Not relevant intervention
Louis R, Joos G, Michils A, Vandenhoven G. A comparison of budesonide/formoterol maintenance and reliever therapy vs. conventional best practice in asthma management. Int J Clin Pract 2009; 63(10):1479-1488.	No	No	Not relevant intervention
Ställberg B, Ekström T, Neij F, et al. A real-life cost-effectiveness evaluation of budesonide/formoterol maintenance and reliever therapy in asthma. Respir Med 2008; 102(10):1360-70.	No	No	Not economic evaluation. The report evaluated direct asthma-related costs.
Shepherd J, Rogers G, Anderson R, et al. Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in adults and children aged 12 years and over. Health Technol Assess 2008; 12(19): iii-iv, 1-360.	No	No	Not relevant information. This report provided a summary of costs and consequences from economic literature and a brief summary of "exploratory model-based" cost-utility analyses for ICS+LABA compared to ICS alone. Given the former and latter, this report did not provide relevant information and was therefore excluded.

Study Reference	Additional Citation From Original Search	Relevant Citation	Reason For Inclusion/Exclusion
Main C, Shepherd J, Anderson R, et al. Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in children under the age of 12 years. Health Technol Assess 2008; 12(20):1-174, iii-iv.	No	No	Not an economic evaluation for the relevant comparators. The report stated: "We have not performed a cost comparison analysis of this research question because we found no reliable evidence that would enable us to conclude, or reasonably assume, equivalence between ICS and ICS plus a LABA."
Lougheed MD, Lemiere C, Ducharme FM et al. Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults. Can Resp J 2012;19:127-164.	Yes	No	Not economic evaluation
Aaron SD, Vandemheen KL, Boulet LP et al. Overdiagnosis of asthma in obese and nonobese adults. Can Med Assoc J 2008;179:1121-31.	Yes	No	Not economic evaluation
Kallstrom TJ, Myers TR. Asthma Disease Management and the Respiratory Therapist. Resp Care 2008;53:770-7.	No	No	Not economic evaluation
Reddel HK, Taylor DR, Bateman ED et al. An Official American Thoracic Society/European Respiratory Society Statement: asthma control and exacerbations. Am J Resp Crit Care Med 2009;180:59-9	No	No	Not economic evaluation
McIvor RA, Boulet LP, Fitzgerald JM, Zimmerman S, Chapman KR. Asthma control in Canada: no improvement since we last looked in 1999. Can Fam Physician 2007;53:672-7.	Yes	No	Not economic evaluation
Guilbert TW, Garris C, Jhingran P et al. Asthma that is not well-controlled is associated with increased health care utilization and decreased quality of life. J Asthma 2011;48:126-32.	Yes	No	Not economic evaluation

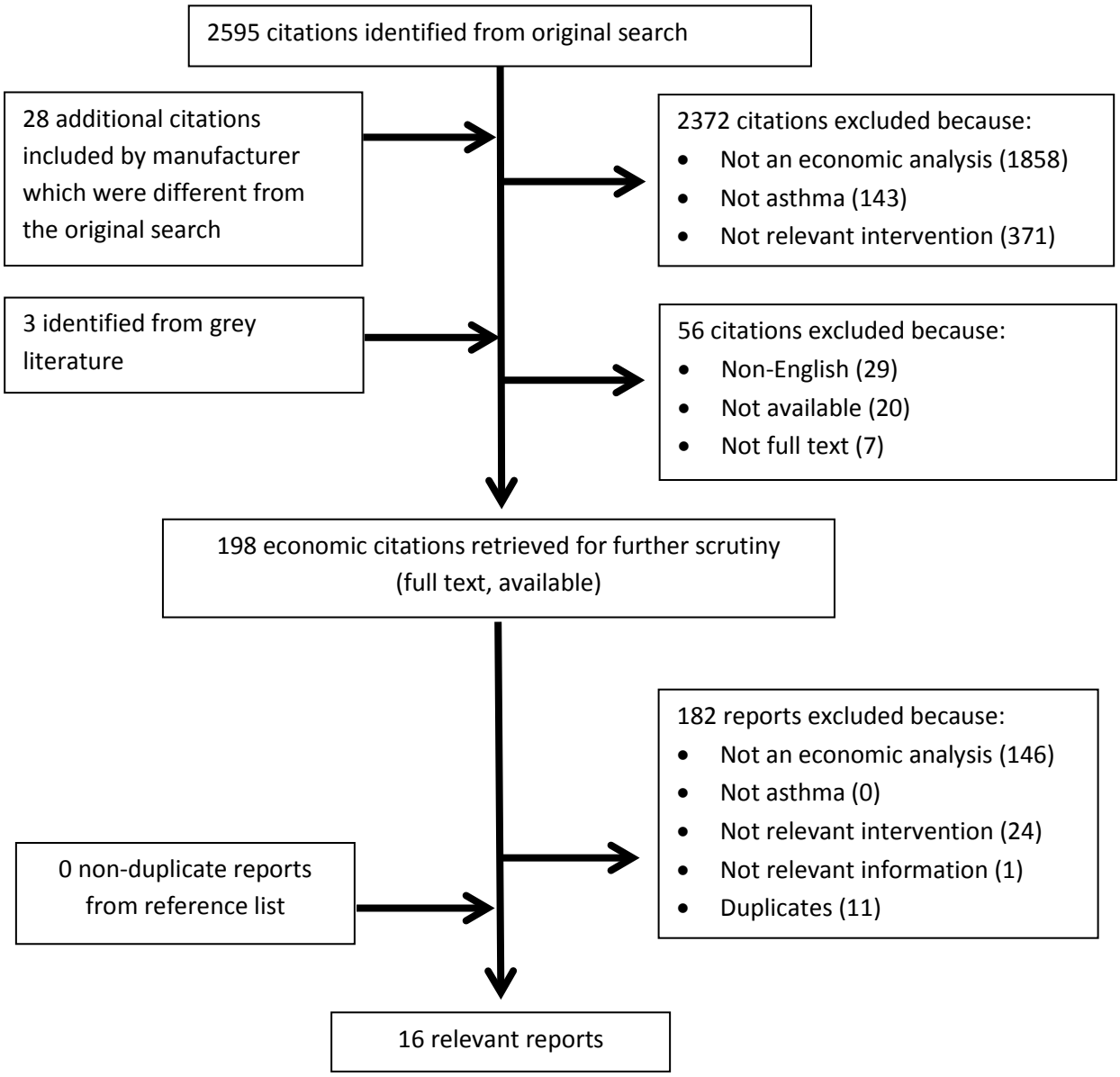
Study Reference	Additional Citation From Original Search	Relevant Citation	Reason For Inclusion/Exclusion
Global Initiative for Asthma. Global Strategy for Asthma Management and prevention. 2014.	Yes	No	Not economic evaluation
Bateman ED, Boushey HA, Bousquet J et al. Can Guideline-defined Asthma control be achieved? Am J Resp Crit Care Med 2004;170:836-44.	Yes	No	Not economic evaluation
Ismaila A, Corriveau D, Vaillancourt J et al. Impact of adherence to treatment with fluticasone propionate/salmeterol in asthma patients. Curr Med Res Opin 2014;1-9.	Yes	No	Not economic evaluation
Ismaila A, Risebrough N, Li C et al. Cost-effectiveness of salmeterol/fluticasone propionate combination (Advair) in uncontrolled asthma in Canada. Resp Med 2014.	Yes	Yes	This report was not identified in the initial search because it was published after the date of the initial search. Therefore, this study is included as a relevant report
Marquis P, Trudea E. Quality of life and patient satisfaction: two important aspects in asthma therapy. Curr Opin Pulm Med 2001;7 (suppl 1):S18-20	Yes	No	Not economic evaluation
O'Connor RD et al. Comparison of patient-reported outcomes during treatment with adjustable- and fixed-dose budesonide/formoterol pressurized metered-dose inhaler versus fixed-dose fluticasone propionate/salmeterol dry powder inhaler in patients with asthma. J ASthma 2010;47:217-33.	Yes	No	Not economic evaluation
Osman LM. How do patients' views about medication affect their self-management in asthma? Patient Educ Couns 1997;32 (1 suppl):S43-9	Yes	No	Not economic evaluation
Adams, RJ et al. Factors associated with hospital admissions and repeat emergency department visits for adults with asthma. Thorax 2000;55:566-73.	Yes	No	Not economic evaluation

Study Reference	Additional Citation From Original Search	Relevant Citation	Reason For Inclusion/Exclusion
Lougheed MD, et al. Canadian Thoracic Society Asthma Management continuum-2010 consensus summary for children 6 years of age and over, and adults. Can Respi J 2010;17:15-24.	Yes	No	Not economic evaluation
LaForce C, et al. Patient satisfaction with a pressurized metered-dose inhaler with an integrated dose counter containing a fixed-dose mometasone furoate/formoterol combination. J Asthma 2011;48:625-31.	Yes	No	Not economic evaluation
Anon. Asthma insight and management in Europe and Canada (EUCAN AIM): a multicountry survey of asthma patients. (proceedings)	Yes	No	Not economic evaluation
Meltzer EO et al. Mometasone furoate/formoterol reduces asthma deteriorations and improves lung function. Eur Respir J 2012;39:279-89.	Yes	No	Not economic evaluation
Nathan RA, et al. Twenty-six-week efficacy and safety study of mometasone furoate/formoterol 200/100 mcg combination treatment in patients with persistent asthma previously receiving medium-dose inhaled corticosteroids. Allergy Asthma Proc 2010;31:269-79.	Yes	No	Not economic evaluation
Weinstein SF, et al. Twelve-week efficacy and safety study of mometasone furoate/formoterol 200/100 mcg and 400/100 mcg combination treatments in patients with persistent asthma previously receiving high-dose inhaled corticosteroids. Allergy Asthma Proc 2010;31:280-9	Yes	No	Not economic evaluation
Bernstein DI, et al. Efficacy and onset of action of mometasone furoate/formoterol and fluticasone propionate/salmeterol combination treatment in subjects with persistent asthma. Allergy Asthma Clin Immunol 2011;721:1-9.	Yes	No	Not economic evaluation

Study Reference	Additional Citation From Original Search	Relevant Citation	Reason For Inclusion/Exclusion
Maspero JF, et al. Long-term safety of mometasone furoate/formoterol combination for treatment of patients with persistent asthma. J Asthma 2010:1-10.	Yes	No	Not economic evaluation
Menezes MB, et al. Inflammatory and functional effects of increasing asthma treatment with formoterol or double dose budesonide. Resp Med 2008;102:1385-91.	Yes	No	Not economic evaluation
O'Byrne PM, et al. Increasing doses of inhaled corticosteroids compared to adding long-acting inhaled beta-agonists in achieving asthma control. Chest 2008;134:1192-99.	Yes	No	Not economic evaluation
Nolte H, et al. Dose-dependent anti-inflammatory effect of inhaled mometasone furoate/formoterol in subjects with asthma. Resp Med 2013;xx:1-9.	Yes	No	Not economic evaluation
Loymans RJ, et al. Comparative effectiveness of long-term drug treatment strategies to prevent asthma exacerbations: network meta-analysis. BMJ 2014;348:g3009.	Yes	No	Not economic evaluation
Gold LS, et al. Asthma control, cost and race: results from a national survey. J Asthma 2013;50:783-90.	Yes	No	Not economic evaluation
Murphy K, et al. Effects of mometasone furoate and formoterol fumarate combination therapy on 4 quality of life domains in patients with moderate asthma. Respirology 2012:17 (suppl 2):1-16	Yes	No	Not economic evaluation
Nathan RA et al. Efficacy and safety of mometasone furoate and formoterol 200/100 mcg twice daily administered via a pressurized metered-dose inhaler in subjects 12 years of age and older with moderate-to-severe asthma. Am J Respir Crit Care Med 2010;181:A5412.	Yes	No	A5412 of volume 181 in 2010 was not available. Nonetheless, given the title, it is likely not an economic evaluation.
Murphy K, et al. Characterization of the effect of mometasone furoate/formoterol treatment on quality of life: an analysis of multi-trial AQLQ findings. J Allergy Clin Immunol 2010:AB196	Yes	No	Not economic evaluation

Appendix A3: Results of Search

This flow chart illustrates the results from the literature search.



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
[40]	Jack A. Radical treatments for difficult times. BMJ (Online). 2009;338(7688):200-1.	Not economic analysis
[41]	Currie GP, Douglas JG, Heaney LG. Difficult to treat asthma in adults. BMJ (Online). 2009;338(7694):593-7.	Not economic analysis
[42]	Williams G. A breath of fresh air. Pharmaceutical Manufacturing and Packing Sourcer. 2013;(AUTUMN):70-4.	Not economic analysis
[43]	Baena-Cagnani CE, Larenas-Linnemann D, Teijeiro A, Canonica GW, Passalacqua G. Will sublingual immunotherapy offer benefit for asthma? Current Allergy and Asthma Reports. 2013;13(6):571-9.	Not economic analysis
[44]	Hasford J. Use long acting beta2 agonists only when asthma cannot be controlled otherwise. BMJ (Online). 2013;347.	Not economic analysis
[45]	Blaiss MS. Over-the-counter intranasal corticosteroids: Why the time is now. Annals of Allergy, Asthma and Immunology. 2013;111(5):316-8.	Not economic analysis
[46]	Currie GP, Small I, Douglas G. Long acting beta2 agonists in adult asthma. BMJ (Online). 2013;347(7927).	Not economic analysis
[47]	James JM. A cost-effectiveness analysis of inhaled corticosteroid delivery for children with asthma in the emergency department. Pediatrics. 2013;132(Suppl1):S44.	Not economic analysis
[48]	Self TH, Paschalis ML, Gulley EC, Mallory LA, Stewart C. Excessive priming of metered-dose inhaler results in poor outcomes. Pediatric Pulmonology. 2013;48(10):1039-40.	Not economic analysis
[49]	Broders J, Desai K, Wilson SA. Help patients control their asthma. Journal of Family Practice. 2013;62(4):184-90.	Not economic analysis
[50]	Mometasone/Formoterol (dulera) for asthma. The Medical letter on drugs and therapeutics. 2010;52(1349):83-4.	Not economic analysis
[51]	Hagiwara M, Delea TE, Stanford RH. Risk of Asthma Exacerbation, Asthma-Related Health Care Utilization and Costs, and Adherence to Controller Therapy in Patients with Asthma Receiving Fluticasone Propionate/Salmeterol Inhalation Powder 100 mug/50 mug Versus Mometasone Furoate Inhalation Powder. Journal of Asthma. 2013;50(3):287-95.	Not economic analysis

Reference #	Study Reference	Reason for exclusion
52	Honkoop PJ, Loymans RJB, Termeer EH, Snoeck-Stroband JB, Bakker MJ, Assendelft WJJ, et al. Asthma control cost-utility randomized trial evaluation (ACCURATE): The goals of asthma treatment. BMC Pulmonary Medicine. 2011;11.	Not economic analysis
53	Perry LE. Pipeline 2011. Drug Topics. 2011;155(1).	Not economic analysis
54	McIvor AR. Inhaler blues? CMAJ. 2011;183(4):464.	Not economic analysis
55	Mometasone/Formoterol (dulera) for asthma. The Medical letter on drugs and therapeutics. 2010;52(1349):83-4.	Not economic analysis
56	Chapman KR, McIvor A. Asthma that is unresponsive to usual care. CMAJ. 2010;182(1):45-52.	Not economic analysis
57	Smith LJ. Anticholinergics for patients with asthma? New England Journal of Medicine. 2010;363(18):1764-5.	Not economic analysis
58	O'Day K, Salamanca-Brosig L, Regan TS, Boswell K, Seal B, Reeder G. Asthma disease burden and formulary decision making: MCO and employer perspectives. Drug Benefit Trends. 2009;21(2):43-9.	Not economic analysis
59	Alexander W, Lage MJ. Beclomethasone-HFA (Qvar) and fluticasone (Flovent) for asthma: Fewer emergencies and lower costs with beclomethasone-HFA. P and T. 2009;34(10):568+574.	Not economic analysis
60	Long-acting beta-2 agonists in asthma. Medical Letter on Drugs and Therapeutics. 2009;51(1303):1-2.	Not economic analysis
61	Louis R, Joos G, Michils A, Vandenhoven G. A comparison of budesonide/formoterol maintenance and reliever therapy vs. conventional best practice in asthma management. International Journal of Clinical Practice. 2009;63(10):1479-88.	Not economic analysis
62	Fanta CH. Drug therapy: Asthma. New England Journal of Medicine. 2009;360(10):1002-14.	Not economic analysis
63	Sears MR. Step-up therapy in uncontrolled asthma: Choices and outcomes. Journal of Allergy and Clinical Immunology. 2009;123(1):122-3.	Not economic analysis
64	Delea TE, Hagiwara M, Stanford RH, Stempel DA. Effects of fluticasone propionate/salmeterol combination on asthma-related health care resource utilization and costs and adherence in children and adults with asthma. Clinical Therapeutics. 2008;30(3):560-71.	Not economic analysis

Reference #	Study Reference	Reason for exclusion
65	Abramowicz M, Zuccotti G, Pflomm J-M, Morey S, Dalton VK, Epstein EJ, et al. Ciclesonide (Alvesco) - A new inhaled corticosteroid for asthma. Medical Letter on Drugs and Therapeutics. 2008;50(1295):75-6.	Not economic analysis
66	Main C, Shepherd J, Anderson R, Rogers G, Thompson-Coon J, Liu Z, et al. Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in children under the age of 12 years. Health Technology Assessment. 2008;12(20):1-123.	Not economic analysis
67	Dinwiddie R. Treatment of acute asthma in children. Which approach is best? Allergologia et Immunopathologia. 2008;36(4):185-6.	Not economic analysis
68	Fritscher L, Chapman KR. Seretide: A pharmacoeconomic analysis. Journal of Medical Economics. 2008;11(3):555-70.	Not economic analysis
69	Brixner DI, Lenhart G, Young DC, Samuelson WM. The effect of fixed combination of fluticasone and salmeterol on asthma drug utilization, asthma drug cost, and episodes of asthma exacerbations. Current Medical Research and Opinion. 2007;23(11):2887-95.	Not economic analysis
70	Gereda JE. Asthma therapy: Is it really cost-effective? Pediatric Allergy and Immunology. 2007;18(5):454.	Not economic analysis
71	Herrick TM, Million RP. Tapping the potential of fixed-dose combinations. Nature Reviews Drug Discovery. 2007;6(7):513-4.	Not economic analysis
72	Harris L, Chertkow J. Fixed dose combinations: A temporary fix or a real solution? Journal of Generic Medicines. 2006;3(3):251-5.	Not economic analysis
73	Niven R. Asthma and mould allergy - Does it matter? Medical Mycology. 2006;44(Suppl 1):257-9.	Not economic analysis
74	Abramson M, Sim MR. Occupational asthma. Thorax. 2006;61(9):741-2.	Not economic analysis
75	Chowdhury BA. Ciclesonide inhalation aerosol for persistent asthma. Journal of Allergy and Clinical Immunology. 2006;117(5):1194-5.	Not economic analysis
76	Mometasone (Asmanex Twisthaler) for asthma. The Medical letter on drugs and therapeutics. 2005;47(1223-1224):98-9.	Not economic analysis
77	Smoot LC. CE: Asthma - Help to promote a breath of fresh air.	Not economic

Reference #	Study Reference	Reason for exclusion
	Drug Topics. 2005;149(18).	analysis
[78]	LoBuono C. New asthma device provides once-daily dosing. Drug Topics. 2005;149(9).	Not economic analysis
[79]	Mometasone (Asmanex Twisthaler) for asthma. Medical Letter on Drugs and Therapeutics. 2005;47(1223-1224):98-9.	Not economic analysis
[80]	Banks JR, Andrews T. Cost-effectiveness analysis of early intervention with budesonide in mild persistent asthma. Pediatrics. 2005;116(2):564-5.	Not economic analysis
[81]	Verma U, Sharma R, Gupta P, Kapoor B, Bano G, Sawhney V. New uses for old drugs: Novel therapeutic options. Indian Journal of Pharmacology. 2005;37(5):279-87.	Not economic analysis
[82]	Todd GRG, Bateman ED. GOAL - Asthma control, but at what cost? (multiple letters). American Journal of Respiratory and Critical Care Medicine. 2005;172(2):254-6.	Not economic analysis
[83]	Wolf BL, Marks A. Largess, excess, and tithing. Journal of Allergy and Clinical Immunology. 2005;115(6):1320-1.	Not economic analysis
[84]	Price D, Haughney J, Lloyd A. Erratum: An economic evaluation of adjustable and fixed dosing with budesonide/formoterol via a single inhaler in asthma patients: The ASSURE study (Current Medical Research and Opinion (2004) 20, 10 (1671-1679) doi:10.1185/030079904X5409). Current Medical Research and Opinion. 2005;21(2):323.	Not economic analysis
[85]	Natarajan A, Davies H. The cost of cure. Archives of Disease in Childhood: Education and Practice Edition. 2004;89(3):ep70-ep75.	Not economic analysis
[86]	O'Connor RD, Stanford R, Crim C, Yancey SW, Edwards L, Rickard KA, et al. Effect of fluticasone propionate and salmeterol in a single device, fluticasone propionate, and montelukast on overall asthma control, exacerbations, and costs. Annals of Allergy, Asthma and Immunology. 2004;93(6):581-8.	Not economic analysis
[87]	Parthasarathi G, Thomas S, Mahesh PA. Choosing an inhaled corticosteriod for asthma: Making an informed decision. Journal of Pharmacy Practice and Research. 2004;34(3):245.	Not economic analysis
[88]	Raisch DW, Holdsworth MT, Marshik PL, Campbell HM. Pharmacoeconomic analysis of therapies for pediatric patients. Expert Review of Pharmacoeconomics and Outcomes Research. 2004;4(5):483-7.	Not economic analysis

Reference #	Study Reference	Reason for exclusion
89	Campbell DA, Robinson DS. Cost advantages of combination asthma therapy. Treatments in Respiratory Medicine. 2004;3(3):133-7.	Not economic analysis
90	Sullivan SD, Buxton M, Andersson LF, Peters J. Budesonide increased symptom free days in patients with recent onset mild asthma at an additional cost of US$0.42/day. Evidence-Based Medicine. 2004;9(3):90.	Not economic analysis
91	Rissmiller RW, Larj MJ, Peters SP, Bleecker ER. Asthma exacerbations and formoterol. Chest. 2004;125(4):1590-1.	Not economic analysis
92	O'Connor RD. Setting the gold standard: clinical and economic decision making in asthma management. Managed care (Langhorne, Pa). 2003;12(1 Suppl):11-7.	Not economic analysis
93	Metcalfe S, Dougherty S, Brougham M, Moodie P. PHARMAC measures savings elsewhere to the health sector. New Zealand Medical Journal. 2003;116(1170).	Not economic analysis
94	McNee W. More on DTCA and the cost of asthma inhalers. New Zealand Medical Journal. 2003;116(1185).	Not economic analysis
95	Saunders B. DTCA and the cost of asthma inhalers. New Zealand Medical Journal. 2003;116(1185).	Not economic analysis
96	Ganderton D, Lewis D, Davies R, Meakin B, Church T. The formulation and evaluation of a CFC-free budesonide pressurised metered dose inhaler. Respiratory Medicine. 2003;97(Suppl D):S4-S9.	Not economic analysis
97	Schuller DE, Zampelli AR. Asthma medications. Journal of Asthma. 2003;40(Suppl):19-22.	Not economic analysis
98	Goeman DP, Sawyer SM, Abramson MJ, Stewart K, Thien FCK, Aroni RA, et al. Inhaled steroids - Too much of a good thing? Medical Journal of Australia. 2003;178(5):247.	Not economic analysis
99	Murphy KR. Cost-effectiveness of pediatric asthma treatments. Journal of Allergy and Clinical Immunology. 2003;111(1):202.	Not economic analysis
100	Clark CE. Use of salmeterol/fluticasone combination (Seretide) in an asthma clinic: A pragmatic open study from primary care. Primary Care Respiratory Journal. 2003;12(3):86-9.	Not economic analysis
101	Budesonide hydrofluoroalkane inhalation - Chiesi: Budesonide HFA inhalation - Chiesi, budesonide Modulite, S 1320 HFA inhalation - Chiesi. Drugs in R and D. 2003;4(1):37-8.	Not economic analysis
102	Zar HJ, Weinberg EG. Treatment of acute asthma - A metered	Not economic

Reference #	Study Reference	Reason for exclusion
	dose inhaler with spacer is an optimal delivery system. South African Medical Journal. 2001;91(8):653-5.	analysis
103	Sullivan SD, Liljas B, Buxton M, Lamm CJ, O'Byrne P, Tan WC, et al. Design and analytic considerations in determining the Cost-Effectiveness of Early Intervention in Asthma from a Multinational Clinical Trial. Controlled Clinical Trials. 2001;22(4):420-37.	Not economic analysis
104	Zetterstrom O, Buhl R, Mellem H, Andersson F. The whole story: Treatment outcomes with Symbicort. Respiratory Medicine. 2002;96(Suppl 1):S29-S35.	Not economic analysis
105	Price D, Haughney J, Duerden M, Nicholls C, Moseley C. Erratum: The cost effectiveness of chlorofluorocarbon-free beclomethasone dipropionate in the treatment of chronic asthma: A cost model based on a 1-year pragmatic, randomised clinical study. (PharmacoEconomics (2002) 20:10 (653-664)). PharmacoEconomics. 2002;20(12):853.	Not economic analysis
106	Thomas M, Stempel DA, Meyer J. Cohorts in economic comparison might not have been comparable (multiple letters). Journal of Allergy and Clinical Immunology. 2002;110(4):670-1.	Not economic analysis
107	Thomas M, Haughney J, Price D. Cost effectiveness of asthma management strategies. PharmacoEconomics. 2002;20(11):789.	Not economic analysis
108	Peters J, Stevenson M, Beverley C, Lim JNW, Smith S. The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: A systematic review and economic evaluation. Health Technology Assessment. 2002;6(5).	Not economic analysis
109	Stoloff S, Poinsett-Holmes K, Dorinsky PM. Combination therapy with inhaled long-acting beta2-agonists and inhaled corticosteroids: A paradigm shift in asthma management. Pharmacotherapy. 2002;22(2 I):212-26.	Not economic analysis
110	Hendeles L, Segal R. Pharmacoeconomic studies of asthma controller drugs: Marketing gimmick or icing on the cake? Pharmacotherapy. 2002;22(2 I):131-3.	Not economic analysis
111	Gustafsson PM. Role of inhaled long-acting beta-agonists. Pediatric Pulmonology. 2001;31(4):323-4.	Not economic analysis
112	McIvor RA. Pharmacoeconomics in pediatric asthma. Chest.	Not economic

Reference #	Study Reference	Reason for exclusion
	2001;120(6):1762-3.	analysis
113	Wang SW, Liu X, Wiener DJ, Sennett C, Bowers BW, Legorreta AP. Comparison of prevalence, cost, and outcomes of a combination of salmeterol and fluticasone therapy to common asthma treatments. American Journal of Managed Care. 2001;7(9):913-22.	Not economic analysis
114	Emerman CL. Managing asthma in the emergency department: Cost-effective strategies. Drug Benefit Trends. 2001;13(8):35-41+46.	Not economic analysis
115	Cada DJ, Levien T, Baker DE. Formoterol fumarate inhalation powder. Hospital Pharmacy. 2001;36(7):753-62.	Not economic analysis
116	Woodcock A, Horice A, Leverard M. CFC transition (multiple letters). Thorax. 2001;56(6):501-2.	Not economic analysis
117	A combination of fluticasone and salmeterol for asthma: Some inhaled drugs for maintenance treatment of chronic asthma. Medical Letter on Drugs and Therapeutics. 2001;43(1102):31-3.	Not economic analysis
118	Chernin T. New asthma combo offers dual approach. Drug Topics. 2001;145(7):24.	Not economic analysis
119	Holimon TD, Chafin CC, Self TH. Nocturnal asthma uncontrolled by inhaled corticosteroids: Theophylline or long-acting beta2 agonists? Drugs. 2001;61(3):391-418.	Not economic analysis
120	Nebulized budesonide for asthma in children. Medical Letter on Drugs and Therapeutics. 2001;43(1096):6-7.	Not economic analysis
121	Markham A, Adkins JC. Inhaled salmeterol/fluticasone propionate combination: A pharmacoeconomic review of its use in the management of asthma. PharmacoEconomics. 2000;18(6):591-608.	Not economic analysis
122	Bradley D. Dual-function medication offers hope for asthma sufferers. Pharmaceutical Science and Technology Today. 2000;3(11):372.	Not economic analysis
123	Rowe BH, Edmonds ML. Inhaled corticosteroids for acute asthma after emergency department discharge. Annals of Emergency Medicine. 2000;36(5):477-80.	Not economic analysis
124	Stempel DA. Economic analysis of asthma practices. American Journal of Managed Care. 2000;6(17 Suppl):S930-S939.	Not economic analysis
125	Senn S, Greig AD, Ram FSF, Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased inhaled steroid or addition of	Not economic analysis

Reference #	Study Reference	Reason for exclusion
	salmeterol in asthma (multiple letters). British Medical Journal. 2000;321(7267):1016-8.	
126	Donohue JF. The expanding role of long-acting beta-agonists. Chest. 2000;118(2):283-5.	Not economic analysis
127	Stempel DA. Pharmacoeconomic impact of inhaled corticosteroids. American Journal of Managed Care. 2000;6(7 Suppl):S382-S387.	Not economic analysis
128	Pieters WR, Lundback B, Johansson G, Palmqvist M, Price MJ, Sondhi S, et al. Cost-effectiveness analyses of salmeterol/fluticasone propionate combination product and fluticasone propionate in patients with asthma II: Study methodologies. PharmacoEconomics. 1999;16(Suppl 2):9-14.	Not economic analysis
129	Lundback B, Pieters WR, Johansson G, Palmqvist M, Price MJ, Sondhi S, et al. Cost-effectiveness analyses of salmeterol/fluticasone propionate combination product and fluticasone propionate in patients with asthma I: Introduction and overview. PharmacoEconomics. 1999;16(Suppl 2):1-8.	Not economic analysis
130	Lim TK. Asthma management: Evidence based studies and their implications for cost-efficacy. Asian Pacific Journal of Allergy and Immunology. 1999;17(3):195-202.	Not economic analysis
131	Bateman E. Salmeterol/fluticasone propionate combination. Drugs. 1999;57(6):941-3.	Not economic analysis
132	Taming the asthma terrain. American Druggist. 1999;216(6):42-7.	Not economic analysis
133	Parker S. Asthma and pregnancy. Australian Prescriber. 1999;22(3):54.	Not economic analysis
134	Hussar DA. Selected new drugs of 1997 (Part III). American Druggist. 1998;215(1):48-55.	Not economic analysis
135	Budesonide turbuhaler for asthma. Medical Letter on Drugs and Therapeutics. 1998;40(1018):15-6.	Not economic analysis
136	Bukstein DA. Incorporating quality of life data into managed care formulary decisions: a case study with salmeterol. The American journal of managed care. 1997;3(11):1701-6.	Not economic analysis
137	I'Epercll K, Rudolf M, Pearson M, Diggle J. General practitioner prescribing habits in asthma/COPD. Asthma in General Practice. 1997;5(2):29-30.	Not economic analysis
138	Lipworth BJ. Treatment of acute asthma. Lancet. 1997;350(9085 Suppl):S18-S23.	Not economic analysis

Reference #	Study Reference	Reason for exclusion
139	Douglass JA, Thien FCK, O'Hehir RE. Immunoteraphy in asthma. Thorax. 1997;52(Suppl 3):S22-S29.	Not economic analysis
140	Stanaszek MB. Asthma pharmacotherapy: Foreword. Journal of Pharmacy Practice. 1997;10(3):130-1.	Not economic analysis
141	Levy DS, Thompson JR, Harding SM, Modrak JB. Flovent (fluticasone propionate inhalation aerosol) (multiple letters). Journal of Allergy and Clinical Immunology. 1997;99(6 I Suppl):861-2.	Not economic analysis
142	Massie RJ, Mellis CM. The economic aspects of drug delivery in asthma. PharmacoEconomics. 1997;11(5):398-407.	Not economic analysis
143	Flaum M, Lung CL, Tinkelman D. Take control of high-cost asthma. Journal of Asthma. 1997;34(1):5-14.	Not economic analysis
144	Rutten-Van Molken MPMH, Kerstjens HAM. Combination of inhaled corticosteroids and beta2-agonists in asthma. Clinical and economic implications. Clinical Immunotherapeutics. 1996;6(6):489-505.	Not economic analysis
145	Fluticasone propionate for chronic asthma. Medical Letter on Drugs and Therapeutics. 1996;38(983):83-4.	Not economic analysis
146	Rees PJ. Oral bronchodilators in the control of asthma. National Medical Journal of India. 1996;9(4):153-4.	Not economic analysis
147	Pingleton SK. Pulmonary medicine. Journal of the American Medical Association. 1996;275(23):1849-50.	Not economic analysis
148	Wasserfallen J-B, Baraniuk JN. Clinical use of inhaled corticosteroids in asthma. Journal of Allergy and Clinical Immunology. 1996;97(1 II):177-82.	Not economic analysis
149	Paris J. Generic inhalers for asthma. Money saved could be spent on patient education. BMJ (Clinical research ed). 1995;310(6979):602.	Not economic analysis
150	Pharmacoeconomic data support early use of inhaled corticosteroids. Drugs and Therapy Perspectives. 1995;6(9):13-6.	Not economic analysis
151	Peters DH, Faulds D. Salmeterol. An appraisal of its quality-of-life benefits and potential pharmacoeconomic positioning in asthma. PharmacoEconomics. 1995;7(6):562-74.	Not economic analysis
152	Strube G, Paris J. Generic inhalers for asthma. British Medical Journal. 1995;310(6979):602.	Not economic analysis
153	Salmeterol: a long-acting beta 2-agonist for asthma. The Nurse practitioner. 1994;19(7):9-10.	Not economic analysis

Reference #	Study Reference	Reason for exclusion
154	Kamada AK, Spahn JD, Blake KV. Salmeterol: Its place in asthma management. Annals of Pharmacotherapy. 1994;28(9):1100-2.	Not economic analysis
155	Ackerman AD. Continuous nebulization of inhaled beta-agonists for status asthmaticus in children: A cost-effective therapeutic advance? Critical Care Medicine. 1993;21(10):1422-4.	Not economic analysis
156	Bailey WC, Clark NM, Gotsch AR, Lemen RJ, O'Connor GT, Rosenstock IM. Asthma prevention. Chest. 1992;102(3 Suppl):216S-31S.	Not economic analysis
157	Costello JF. Asthma - A United Kingdom view; Treatment and its implications. Annals of the New York Academy of Sciences. 1991;629()(pp 7-14), 1991. Date of Publication: 1991.):7-14.	Not economic analysis
158	Ruggeri I, Bragato D, Colombo GL, Valla E, Di MS. Cost and appropriateness of treating asthma with fixed-combination drugs in local health care units in Italy. ClinicoEcon. 2012;outcomes res.. 4:375-82, 2012.:-82. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3519004	Not economic analysis
159	Canadian Agency for Drugs and Technologies in Health (CADTH). Long-acting beta(2)-agonist and inhaled corticosteroid combination therapy for adult persistent asthma: systematic review of clinical outcomes and economic evaluation. CADTH Technol Overv. 2010;1(3):e0120, 2010. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3411155	Not economic analysis
160	Legorreta AP. Costs associated with common dual-controller therapies for treating asthma in several managed care populations. J Manage Care Pharm. 2002 Sep;8(5 Suppl):18-21.	Not economic analysis
161	Honkoop PJ, Loymans RJ, Termeer EH, Snoeck-Stroband JB, Bakker MJ, Assendelft WJ, et al. Asthma control cost-utility randomized trial evaluation (ACCURATE): the goals of asthma treatment. BMC polm. 2011;med.. 11:53, 2011. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3295696	Not economic analysis
162	Mometasone/Formoterol (dulera) for asthma. Med Lett Drugs Ther. 2010 Oct 18;52(1349):83-4.	Not economic analysis
163	Anthonisen NR. Economic evaluations. Can Respir J. 2007	Not economic

Reference #	Study Reference	Reason for exclusion
	Jul;14(5):264-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2676388	analysis
164	McNee W. More on DTCA and the cost of asthma inhalers. N z med j. 2003 Nov 7;116(1185):U673, 2003.	Not economic analysis
165	Budesonide turbuhaler for asthma. Med Lett Drugs Ther. 1998 Jan 16;40(1018):15-6.	Not economic analysis
166	Hagiwara M, Delea TE, Stanford RH. Health-care utilization and costs with fluticasone propionate and fluticasone propionate/salmeterol in asthma patients at risk for exacerbations. Allergy Asthma Proc. 2014 Jan;35(1):54-62.	Not economic analysis
167	Hagiwara M, Delea TE, Stanford RH. Risk of asthma exacerbation, asthma-related health care utilization and costs, and adherence to controller therapy in patients with asthma receiving fluticasone propionate/salmeterol inhalation powder 100 mug/50 mug versus mometasone furoate inhalation powder. J Asthma. 2013 Apr;50(3):287-95.	Not economic analysis
168	Stanford RH, Riedel AA, Johnson JC, Astry CL. Comparative resource utilization in medicaid-eligible patients with asthma treated with fixed-dose fluticasone propionate/salmeterol or fluticasone propionate monotherapy. Clinical Therapeutics. 2010;32(10):1782-93.	Not economic analysis
169	O'Connor RD, Stanford R, Crim C, Yancey SW, Edwards L, Rickard KA, et al. Effect of fluticasone propionate and salmeterol in a single device, fluticasone propionate, and montelukast on overall asthma control, exacerbations, and costs. Annals of Allergy, Asthma and Immunology. 2004;93(6):581-8.	Not economic analysis
170	Louis R, Joos G, Michils A, Vandenhoven G. A comparison of budesonide/formoterol maintenance and reliever therapy vs. conventional best practice in asthma management. Int J Clin Pract. 2009 Oct;63(10):1479-88. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2780558	Not economic analysis
171	Clark CE. Use of salmeterol/fluticasone combination (Seretide) in an asthma clinic: A pragmatic open study from primary care. 13 2003 Sep.	Not economic analysis
172	National Institute for Health and Clinical Excellence. Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years. National Institute for Health and	Not economic analysis

Reference #	Study Reference	Reason for exclusion
	Clinical Excellence; 2007. Report No.: 131	
173	National Institute for Health and Clinical Excellence. Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over. National Institute for Health and Clinical Excellence; 2008. Report No.: 138	Not economic analysis
174	Stanciole AE, Ortegon M, Chisholm D, Lauer JA. Cost effectiveness of strategies to combat chronic obstructive pulmonary disease and asthma in sub-Saharan Africa and South East Asia: mathematical modelling study. BMJ (Clinical research ed). 2012;344:e608.	Not relevant intervention
175	Quirce S, Barcina C, Plaza V, Calvo E, Muoz M, Ampudia R, et al. A comparison of budesonide/formoterol maintenance and reliever therapy versus conventional best practice in asthma management in spain. Journal of Asthma. 2011;48(8):839-47.	Not relevant intervention
176	Manson SC, Brown RE, Cerulli A, Vidaurre CF. The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. Respiratory Medicine. 2009;103(7):975-94.	Not relevant intervention
177	Sears MR, Boulet L-P, Laviolette M, FitzGerald JM, Bai TR, Kaplan A, et al. Budesonide/formoterol maintenance and reliever therapy: Impact on airway inflammation in asthma. European Respiratory Journal. 2008;31(5):982-9.	Not relevant intervention
178	Price D, Wiren A, Kuna P. Cost-effectiveness of budesonide/formoterol for maintenance and reliever asthma therapy (Allergy: European Journal of Allergy and Clinical Immunology (2007) 62, (1189-1198)). Allergy: European Journal of Allergy and Clinical Immunology. 2008;63(7):951.	Not relevant intervention
179	Trautmann M, Banik N, Tews JT, Jorres RA, Nowak D. Efficacy of the combination of fluticasone propionate and salmeterol in patients with moderate persistent asthma within a "real-life" setting. European Journal of Medical Research. 2007;12(6):255-63.	Not relevant intervention
180	Simonella L, Marks G, Sanderson K, Andrews G. Cost-effectiveness of current and optimal treatment for adult asthma. Internal Medicine Journal. 2006;36(4):244-50.	Not relevant intervention
181	Miyagawa T, Arakawa I, Shiragami M, Nishimura S. Cost-effectiveness of including salmeterol in asthma therapy in a primary care setting in Japan. Yakugaku Zasshi.	Not relevant intervention

Reference #	Study Reference	Reason for exclusion
	2006;126(1):51-9.	
182	Sullivan SD, Buxton M, Andersson LF, Lamm CJ, Liljas B, Chen YZ, et al. Cost-effectiveness analysis of early intervention with budesonide in mild persistent asthma. Journal of Allergy and Clinical Immunology. 2003;112(6):1229-36.	Not relevant intervention
183	Everden P, Lloyd A, Hutchinson J, Plumb J. Cost-effectiveness of eformoterol Turbohaler versus salmeterol Accuhaler in children with symptomatic asthma. Respiratory Medicine. 2002;96(4):250-8.	Not relevant intervention
184	Plaza V, Serra-Batlles J, Ferrer M, Morejon E. Quality of life and economic features in elderly asthmatics. Respiration. 2000;67(1):65-70.	Not relevant intervention
185	Price DB, Cargill K, Wolfe S, Darby H. Salmeterol xinafoate: An analysis of outcomes and cost-effectiveness using a primary care database. Respiratory Medicine. 1998;92(11):1302-4.	Not relevant intervention
186	Price DB, Appleby JL. Fluticasone propionate: An audit of outcomes and cost-effectiveness in primary care. Respiratory Medicine. 1998;92(2):351-3.	Not relevant intervention
187	O'Byrne P, Cuddy L, Wayne TD, Birch S, Morris J, Syrotuik J. Efficacy and cost benefit of inhaled corticosteroids in patients considered to have mild asthma in primary care practice. Canadian Respiratory Journal. 1996;3(3):169-75.	Not relevant intervention
188	Stanciole AE, Ortegon M, Chisholm D, Lauer JA. Cost effectiveness of strategies to combat chronic obstructive pulmonary disease and asthma in sub-Saharan Africa and South East Asia: mathematical modelling study. BMJ (Clinical research ed). 2012;344:e608.	Not relevant intervention
189	Quirce S, Barcina C, Plaza V, Calvo E, Munoz M, Ampudia R, et al. A comparison of budesonide/formoterol maintenance and reliever therapy versus conventional best practice in asthma management in Spain. J Asthma. 2011 Oct;48(8):839-47.	Not relevant intervention
17	Sears MR, Boulet LP, Laviolette M, FitzGerald JM, Bai TR, Kaplan A, et al. Budesonide/formoterol maintenance and reliever therapy: impact on airway inflammation in asthma. Eur Respir J. 2008 May;31(5):982-9.	Not relevant intervention
190	Trautmann M, Banik N, Tews JT, Jorres RA, Nowak D. Efficacy of the combination of fluticasone propionate and salmeterol in patients with moderate persistent asthma within a "real-	Not relevant intervention

Reference #	Study Reference	Reason for exclusion
	life" setting. European Journal of Medical Research. 2007;12(6):255-63.	
191	Simonella L, Marks G, Sanderson K, Andrews G. Cost-effectiveness of current and optimal treatment for adult asthma. Intern Med J. 2006 Apr;36(4):244-50.	Not relevant intervention
18	Weiss K, Buxton M, Andersson FL, Lamm CJ, Liljas B, Sullivan SD. Cost-effectiveness of early intervention with once-daily budesonide in children with mild persistent asthma: results from the START study. Pediatr Allergy Immunol. 2006 May;17 Suppl 17:21-7.	Not relevant intervention
192	Miyagawa T, Arakawa I, Shiragami M, Nishimura S. Cost-effectiveness of including salmeterol in asthma therapy in a primary care setting in Japan. Journal of the Pharmaceutical Society of Japan. 2006;126(1).	Not relevant intervention
193	Sullivan SD, Buxton M, Andersson LF, Lamm CJ, Liljas B, Chen YZ, et al. Cost-effectiveness analysis of early intervention with budesonide in mild persistent asthma. Journal of Allergy and Clinical Immunology. 2003;112(6):1229-36.	Not relevant intervention
194	Price DB, Appleby JL. Fluticasone propionate: An audit of outcomes and cost-effectiveness in primary care. Respiratory Medicine. 1998;92(2):351-3.	Not relevant intervention
195	Marchetti M, Cavallo M, Annoni E, Gerzeli S. Cost-utility of inhaled corticosteroids in patients with moderate-to-severe asthma. Expert Rev Pharmacoecon Outcomes Res. 2004 Oct;4(5):549-64.	Not relevant intervention
27	Shepherd J, Rogers G, Anderson R, Main C, Thompson-Coon J, Hartwell D, et al. Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in adults and children aged 12 years and over. Health Technology Assessment. 2008;12(19):1-233.	Not relevant information
196	Lundback B, Jenkins C, Price MJ, Thwaites RM. Cost-effectiveness of salmeterol/fluticasone propionate combination product 50/250 microg twice daily and budesonide 800 microg twice daily in the treatment of adults and adolescents with asthma. International Study Group. Respir Med. 2000 Jul;94(7):724-32.	Duplicate

Reference #	Study Reference	Reason for exclusion
197	Wickstrom J, Dam N, Malmberg I, Hansen BB, Lange P. Cost-effectiveness of budesonide/formoterol for maintenance and reliever asthma therapy in Denmark--cost-effectiveness analysis based on five randomised controlled trials. Clin Respir J. 2009 Jul;3(3):169-80.	Duplicate
198	Shih YC, Mauskopf J, Borker R. A cost-effectiveness analysis of first-line controller therapies for persistent asthma. PharmacoEconomics. 2007;25(7):577-90.	Duplicate
199	Doull I, Price D, Thomas M, Hawkins N, Stamuli E, Tabberer M, et al. Cost-effectiveness of salmeterol xinafoate/fluticasone propionate combination inhaler in chronic asthma. Curr Med Res Opin. 2007 May;23(5):1147-59.	Duplicate
200	Briggs AH, Bousquet J, Wallace MV, Busse WW, Clark TJ, Pedersen SE, et al. Cost-effectiveness of asthma control: an economic appraisal of the GOAL study. Allergy. 2006 May;61(5):531-6.	Duplicate
19	Jonsson B, Berggren F, Svensson K, O'Byrne PM. An economic evaluation of combination treatment with budesonide and formoterol in patients with mild-to-moderate persistent asthma. Respir Med. 2004 Nov;98(11):1146-54.	Duplicate
201	Price MJ, Briggs AH. Development of an economic model to assess the cost effectiveness of asthma management strategies. PharmacoEconomics. 2002;20(3):183-94.	Duplicate
202	Andersson F, Stahl E, Barnes PJ, Lofdahl C-G, O'Byrne PM, Pauwels RA, et al. Adding formoterol to budesonide in moderate asthma - Health economic results from the FACET study. Respiratory Medicine. 2001;95(6):505-12.	Duplicate
203	Lundback B, Jenkins C, Price MJ, Thwaites RM. Cost-effectiveness of salmeterol/fluticasone propionate combination product 50/250 microg twice daily and budesonide 800 microg twice daily in the treatment of adults and adolescents with asthma. International Study Group. Respir Med. 2000 Jul;94(7):724-32.	Duplicate
204	Doull I, Price D, Thomas M, Hawkins N, Stamuli E, Tabberer M, et al. Cost-effectiveness of salmeterol xinafoate/fluticasone propionate combination inhaler in chronic asthma Current Medical Research and Opinion. 2007;23(5):1147-59.	Duplicate
205	Briggs AH, Bousquet J, Wallace MV, Busse WW, Clark TJH,	Duplicate

Reference #	Study Reference	Reason for exclusion
	Pedersen SE, et al. Cost-effectiveness of asthma control: An economic appraisal of the GOAL study. Allergy: European Journal of Allergy and Clinical Immunology. 2006;61(5):531-6.	

Appendix A5: List of Included Studies

The following table lists the studies included within the review.

Reference #	Study Reference
4	Wickstrom J, Dam N, Malmberg I, Hansen BB, Lange P. Cost-effectiveness of budesonide/formoterol for maintenance and reliever asthma therapy in Denmark - Cost-effectiveness analysis based on five randomised controlled trials. Clinical Respiratory Journal. 2009;3(3):169-80.
16	Shih Y-C, Mauskopf J, Borker R. A cost-effectiveness analysis of first-line controller therapies for persistent asthma. PharmacoEconomics. 2007;25(7):577-90.
5	Doull I, Price D, Thomas M, Hawkins N, Stamuli E, Tabberer M, et al. Cost-effectiveness of salmeterol xinafoate/fluticasone propionate combination inhaler in chronic asthma. Current Medical Research and Opinion. 2007;23(5):1147-59.
6	Briggs AH, Bousquet J, Wallace MV, Busse WW, Clark TJH, Pedersen SE, et al. Cost-effectiveness of asthma control: An economic appraisal of the GOAL study. Allergy: European Journal of Allergy and Clinical Immunology. 2006;61(5):531-6.
7	Ericsson K, Bantje TA, Huber RM, Borg S, Bateman ED. Cost-effectiveness analysis of budesonide/formoterol compared with fluticasone in moderate-persistent asthma. Respiratory Medicine. 2006;100(4):586-94.
9	Jonsson B, Berggren F, Svensson K, O'Byrne PM. An economic evaluation of combination treatment with budesonide and formoterol in patients with mild-to-moderate persistent asthma. Respiratory Medicine. 2004;98(11):1146-54.
8	Price MJ, Briggs AH. Development of an economic model to assess the cost effectiveness of asthma management strategies. PharmacoEconomics. 2002;20(3):183-94.
10	Andersson F, Stahl E, Barnes PJ, Lofdahl C-G, O'Byrne PM, Pauwels RA, et al. Adding formoterol to budesonide in moderate asthma - Health economic results from the FACET study. Respiratory Medicine. 2001;95(6):505-12.
11	Lundback B, Jenkins C, Price MJ, Thwaites RMA. Cost-effectiveness of salmeterol/fluticasone propionate combination product 50/250 mug twice daily and budesonide 800 mug twice daily in the treatment of adults and adolescents with asthma. Respiratory Medicine. 2000;94(7):724-32.

Reference #	Study Reference
13	Pieters WR, Lundback B, Sondhi S, Price MJ, Thwaites RMA. Cost-effectiveness analysis of salmeterol/fluticasone propionate 50/500mug vs fluticasone propionate 500mug in patients with corticosteroid- dependent asthma V: Results. PharmacoEconomics. 1999;16(Suppl 2):29-34.
12	Palmqvist M, Price MJ, Sondhi S. Cost-effectiveness analysis of salmeterol/fluticasone propionate 50/250mug vs fluticasone propionate 250mug in adults and adolescents with asthma IV: Results. PharmacoEconomics. 1999;16(Suppl 2):23-8.
14	Johansson G, Price MJ, Sondhi S. Cost-effectiveness analysis of salmeterol/fluticasone propionate 50/100mug vs fluticasone propionate 100mug in adults and adolescents with asthma III: Results. PharmacoEconomics. 1999;16(Suppl 2):15-21.
2	Lenney W, McKay AJ, Tudur SC, Williamson PR, James M, Price D, et al. Management of Asthma in School age Children On Therapy (MASCOT): a randomised, double-blind, placebo-controlled, parallel study of efficacy and safety. Health Technol Assess. 2013 Feb;17(4):1-218.
3	Goossens LM, Riemersma RA, Postma DS, van der MT, Rutten-van Molken MP. An economic evaluation of budesonide/formoterol for maintenance and reliever treatment in asthma in general practice. Adv Ther. 2009 Sep;26(9):872-85.
1	Bond K, Coyle D, O'Gorman K, Coyle K, Spooner C, Lemière C, et al. Long-Acting Beta2-Agonist and Inhaled Corticosteroid Combination Therapy for Adult Persistent Asthma: Systematic Review of Clinical Outcomes and Economic Evaluation. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009. Report No.: 122
15	Ismaila AS, Risebrough N, Li C, Corriveau D, Hawkins N, FitzGerald JM, et al. COST-effectiveness of salmeterol/fluticasone propionate combination (Advair) in uncontrolled asthma in Canada. Respir Med. 2014 Jun 25.

Appendix A6: Characteristics of Reviewed Studies

The following tables list characteristics of reviewed studies.

Study	Ismaila et al. (2014)
Sponsorship	GlaxoSmithKline
Country	Canada
Perspective	Health care system perspective
Study type	CUA
Comparators	ICS (fluticasone propionate 200 µg, 400-500 µg, 1000 µg daily) ICS+LABA (salmeterol xinafoate/ fluticasone propionate 200 µg, 500 µg, 1000 µg daily)
ICS dosage	fluticasone propionate: 200 µg (low), 400-500 µg (medium), 100h µg (high)
Populations	Adolescent and adult patients with uncontrollable asthma Aged 12and older
Time horizon	1 year
Type of model	Decision analytic model
Cycle length	N/A
Efficacy inputs	Symptom-free day QALY
Adverse events	No included
Utilities	AQLQ mapped to EQ-5D
Discounting	N/A
Outcomes	Incremental cost per QALY
Results	ICURs for ICS+LABA compared to same dose were $43,981 per QALY (low dose ICS), $42,911 per QALY (medium dose ICS), and $54,411 per QALY (high dose ICS) ICURs for ICS+LABA compared to increased dose were $24,959 per QALY (medium dose ICS) and $3,432 per QALY (high dose ICS)
Types of sensitivity analysis	Deterministic sensitivity analysis (one-way) Efficacy Utility Non-drug costs Deterministic sensitivity analysis (scenario) Hospitalization costs from Ontario as opposed to Alberta Probabilistic sensitivity analysis (Monte Carlo simulation) Treatment effect (normal distribution) Non-drug cost (normal distribution) Utilities (normal distribution)

Study	Ismaila et al. (2014)
Sensitivity analysis results	Deterministic sensitivity analysis (one-way) Results were sensitive to efficacy Deterministic sensitivity analysis (scenario) Results were insensitive to scenario using hospitalization costs from Ontario as opposed to Alberta Probabilistic sensitivity analysis (Monte Carlo simulation) At a willingness to pay of $50,000 per QALY, the probability of ICS+LABA being cost effective compared to similar dose ICS was 77% (low dose ICS), 78% (medium dose ICS), and 39% (high dose ICS) At a willingness to pay of $50,000 per QALY, the probability of ICS+LABA being cost effective compared to increased dose ICS was 86% (medium dose ICS) and 99% (high dose ICS)
Points to consider	Costs(2011$CAN) Decision analytic modelEfficacy data derived from meta-analysis Final outcomes considered Utility values derived from AQLQ scores mapped to EQ-5D

Study	Bond et al., 2009
Sponsorship	CADTH
Country	Canada
Perspective	Government perspective
Study type	CEA/CUA
Comparators	LABA plus ICS ICS
Populations	Adolescents and adults with asthma were divided in one of three categories: steroid naïve patients, low dose ICS users, and medium dose ICS users Age 12 and older
ICS dosage	fluticasone propionate via metered dose inhaler: ≤250 mcg daily (low), 251-500 mcg daily (medium), >500 mcg daily (high) fluticasone propionate diskus: ≤250 mcg daily (low), 251-500 mcg daily (medium), >500 mcg daily (high) budesonide turbuhaler: ≤400 mcg daily (low), 400-800 mcg daily (medium), >800 mcg daily (high) beclomethasone dipropionate: ≤500 mcg daily (low), 501-1000 mcg daily (medium), >1000 mcg daily (high)

Study	Bond et al., 2009
Time horizon	12 weeks
Type of model	Markov Model
Cycle length	1 week
Efficacy inputs	QALY Exacerbations avoided Successfully controlled week
Adverse events	Not included
Utilities	Published literature
Discounting	N/A
Outcomes	Incremental cost per QALY gained Incremental cost per exacerbation avoided Incremental cost per successfully controlled week
Results	For steroid naïve patients, the incremental cost-effectiveness ratios of ICS plus LABA compared to ICS alone were $3.3 million per QALY, $13,385 per exacerbation avoided, and $1,375 per additional controlled weeks For patients with asthma that is uncontrolled with low dose ICS, the incremental cost-effectiveness ratios of ICS plus LABA compared to medium dose of ICS were $1.6 million per QALY, and $6,608 per exacerbation avoided, $476 per additional controlled weeks For patients with asthma that is uncontrolled with medium dose ICS, the incremental cost-effectiveness ratios of ICS plus LABA compared to high dose of ICS were $0.19 million per QALY, and $787 per exacerbation avoided, and $57 per additional controlled weeks
Types of sensitivity analysis	<u>Deterministic analysis (one-way)</u> Time horizon Assumption different rate of exacerbations managed through self-care Assumption LABA-ICS reduces proportion of exacerbations requiring medical management Utilities Costs of exacerbations Relative risks for step up and for exacerbation Assumption no step down on monotherapy <u>Probabilistic analysis (Monte Carlo simulation)</u> Transition probabilities (beta distribution) Costs (gamma distribution) Utilities (log normal) Treatment effect (log normal)

Study	Bond et al., 2009
Sensitivity analysis results	Deterministic analysis (one-way) Results insensitive to changes to time horizon, utilities, costs of exacerbations, and relative risks for step up and for exacerbation, and assumptions regarding different rate of exacerbations managed through self-care, LABA-ICS reduction in the proportion of exacerbations requiring medical management, and no step down on monotherapy Probabilistic analysis (Monte Carlo simulation) At a willingness to pay of $50,000 per QALY, ICS plus LABA compared to high dose of ICS had the highest probability of being cost effective
Points to consider	Costs CDN$ (2008) Effectiveness data derived from a meta-analysis Utility values derived from a UK National Institute for Health Research report Extensive sensitivity analysis Probabilistic analysis considered appropriate distributions

Study	Lenney et al., 2013
Sponsorship	NIHR Health Technology Assessment Programme
Country	UK
Perspective	Health service perspective
Study type	CUA
Comparators	ICS+LABA (fluticasone propionate 100 µg/salmeterol 50 µg twice a day plus placebo once a day) ICS (fluticasone propionate 100 µg twice a day plus placebo once a day)
ICS dosage	fluticasone propionate: 100 µg twice a day (low)
Populations	Children and adolescents with asthma Aged 6-14
Time horizon	48 weeks
Type of model	Trial based analysis
Cycle length	N/A
Efficacy inputs	Number of asthma exacerbations requiring treatment with oral corticosteroids QALY
Adverse events	Not included
Utilities	PAQLQ scores
Discounting	N/A
Outcomes	Incremental cost utility ratio
Results	ICUR for ICS+LABA compared to ICS was £12,054 per QALY
Types of sensitivity analysis	Non-parametric bootstrap 2000 iterations

Study	Lenney et al., 2013
Sensitivity analysis results	The probability of ICS+LABA being cost effective compared to ICS was 60%
Points to consider	Costs £ (2010-11) Efficacy data derived from RCT Children population (Ages 6-14) Adverse events not included Utility value derived from PAQLQ Limited SA Comparison of monotherapy to combination therapy

Study	Goossens et al. (2009)
Sponsorship	AstraZeneca
Country	Netherlands
Perspective	Societal perspective
Study type	CEA
Comparators	ICS+LABA [Symbicort (budesonide 100 µg /formoterol 6 µg)] once daily, plus as needed Usual care [low or medium daily doses ICS (≤800 µg budesonide/beclomethasone or ≤500 µg fluticasone)] plus SABA if needed
ICS dosage	Budesonide: ≤800 µg daily (low-medium) Beclomethasone: ≤800 µg daily (low-medium) Fluticasone : ≤500 µg daily (low-medium)
Populations	Patients with mild to moderate asthma (NHG guidelines) Age 18 years and older
Time horizon	1 year
Type of model	Trial based analysis (using bootstrap method)
Cycle length	N/A
Efficacy inputs	Proportion of asthma-control days ACQ score
Adverse events	Not included
Utilities	N/A
Discounting	N/A
Outcomes	Incremental cost per asthma-control days Incremental cost per net proportion of improved patients Incremental cost per improvement in ACQ score Incremental cost per proportion of well-controlled patients

Study	Goossens et al. (2009)
Results	Results presented in cost-effectiveness planes Results from bootstrap replications suggest that ICS+LABA would lead to cost savings compared to usual care. Results varied by health outcome, and results were not statistically significant. Incremental cost per asthma-control days and cost per net proportion of well-controlled patients cost savings and smaller health benefits compared to ICS, while , the incremental cost per improvement in ACQ score and per net proportion of improved patients for ICS+LABA would lead to cost savings and greater health benefits compared to ICS.
Types of sensitivity analysis	Deterministic analysis (one-way) Productivity losses ACQ score Assumption of defined well-controlled asthma based on the ACQ
Sensitivity analysis results	Results were sensitive to the inclusion of productivity losses for every patient. Results were insensitive to ACQ score calculation or well-controlled asthma assumption.
Points to consider	Costs €(2007) Efficacy data derived from RCT Trial based analysis (using bootstrap method) Results presented in cost-effectiveness planes Final outcomes not considered Comparison of ICS+LABA as maintenance and reliever versus usual care (ICS) plus reliever as needed

Study	Wickstrøm et al. (2009)
Sponsorship	AstraZeneca
Country	Denmark
Perspective	Health care system perspective Societal perspective
Study type	CEA
Comparators	ICS+LABA (budesonide 80 µg /formoterol 4.5 µg) twice a day as maintenance and reliever ICS+LABA (budesonide 80 µg /formoterol 4.5 µg) twice a day plus SABA as needed ICS (budesonide 320 µg) twice a day plus SABA as needed
ICS dosage	Budesonide: 320 µg twice a day (low)
Populations	Patients asthma (severity not specified) Age 4-80 years
Time horizon	1 year
Type of model	Trial based analysis

Study	Wickstrøm et al. (2009)
Cycle length	N/A
Efficacy inputs	Number of severe exacerbation avoided per patient per year
Adverse events	Not included
Utilities	N/A
Discounting	N/A
Outcomes	Incremental cost per exacerbation avoided
Results	Results suggest that ICS+LABA as maintenance and reliever dominated ICS plus SABA as needed.
Types of sensitivity analysis	Deterministic analysis (one-way) Cost of medication Cost of hospitalization Total direct costs
Sensitivity analysis results	Results were insensitive to changes in costs (cost of medication, cost of hospitalization or total direct costs)
Points to consider	Costs €(2007); DDK1=€0.134 Efficacy data derived from RCT Trial based analysis Final outcomes not considered Comparison of ICS+LABA as maintenance and reliever as needed versus (ICS) plus SABA as needed

Study	Doull et al., 2007
Sponsorship	GlaxoSmithKline
Country	UK
Perspective	Health care system perspective
Study type	CUA
Comparators	ICS+LABA (salmeterol xinafoate 100 µg/ fluticasone 200 µg, salmeterol xinafoate 100 µg/ fluticasone 500 µg) via Accuhaler and Evohaler ICS [fluticasone propionate 200 µg daily, fluticasone propionate 500µg daily, beclometasone dipropionate 1000 µg daily, beclometasone dipropionate 2000 µg daily]
ICS dosage	fluticasone propionate: 200 µg daily (low), 500µg daily (medium) beclometasone dipropionate: 1000 µg daily (high*), 2000 µg daily (high**) *considered low dose in analysis ** considered medium dose in analysis
Populations	Patients under 12 years of age with asthma Patients aged 12 and over with asthma
Time horizon	1 year
Type of model	Decision analytic model

Study	Doull et al., 2007
Cycle length	N/A
Efficacy inputs	Symptom-free days
Adverse events	Not included
Utilities	AQLQ scores mapped to EQ-5D
Discounting	N/A
Outcomes	Incremental cost per QALY
Results	Patients aged 12 and over (low dose) ICUR for ICS+LABA (salmeterol/fluticasone propionate) via Accuhaler compared to low dose ICS (fluticasone propionate) was £6,852 per QALY and via Evohaler, ICS+LABA dominated ICS ICUR for ICS+LABA (salmeterol/fluticasone propionate) compared to low dose ICS (beclometasone dipropionate) was £15,997 per QALY via Accuhaler and £5,679 per QALY via Evohaler. Patients aged 12 and over (medium dose) ICUR for ICS+LABA (salmeterol/fluticasone propionate) dominated medium dose ICS (fluticasone propionate) ICUR for ICS+LABA (salmeterol/fluticasone propionate) compared to medium dose ICS (beclometasone dipropionate) was £14,567 per QALY Patients under 12 years of age (low dose) ICUR for ICS+LABA compared to low dose ICS (fluticasone propionate) was £63,736 per QALY via Accuhaler; and £15,739 per QALY via Evohaler
Types of sensitivity analysis	Probabilistic analysis (Monte Carlo simulation) Treatment effect (normal distribution) Costs (normal distribution) Utilities (normal distribution)
Sensitivity analysis results	Probabilistic analysis (Monte Carlo simulation) At a willingness to pay of £20,000 per QALY, the probability of ICS+LABA via Evohaler being cost effective compared to low dose ICS in asthma patients aged 12 and over (fluticasone propionate) was 0.90, compared to medium dose was 1.00, and compared to low dose in children under 12 was 0.03
Points to consider	Costs £(2006) Decision analytic model Effectiveness data derived from meta-analysis Utility values derived from AQLQ scores mapped to EQ-5D DSA not conducted Final outcomes (QALY) considered

Study	Shih et al., 2007
Sponsorship	GlaxoSmithKline
Country	USA
Perspective	US Payer in managed care organization perspective
Study type	CEA

Study	Shih et al., 2007
Comparators	ICS+LABA (salmeterol 50 µg/fluticasone propionate 100 µg) ICS (fluticasone propionate, dosages vary)
ICS dosage	fluticasone propionate: not specified
Populations	Patients with mild to moderate asthma Aged 12 and over
Time horizon	1 year
Type of model	Decision analytic model
Cycle length	N/A
Efficacy inputs	Symptom-free day Rescue medication-free day
Adverse events	Not included
Utilities	N/A
Discounting	N/A
Outcomes	Incremental cost per symptom-free day Incremental cost per rescue medication-free day
Results	ICERs for ICS+LABA compared to ICS (-fluticasone propionate) were $9.55 per symptom-free day and $8.93 per rescue medication-free day ICS+LABA compared to ICS (non-fluticasone propionate) were not presented
Types of sensitivity analysis	Deterministic Sensitivity Analysis (one-way) Adherence Adherence – effectiveness assumption Probabilistic analysis (Monte Carlo simulation) Transition probabilities (Dirichlet distribution, Beta distribution) Costs (triangular distribution) Discounting (uniform distribution)
Sensitivity analysis results	Deterministic Sensitivity Analysis (one-way) Results insensitive to changes to adherence and to adherence-effectiveness assumptions Probabilistic analysis (Monte Carlo simulation) At a willingness to pay of $14.80 per symptom-free day, ICS+LABA has 98% probability of being cost effective compared to ICS (fluticasone propionate)
Points to consider	Costs USD$(2005) Decision analysis model Effectiveness data derived from RCTs Inappropriate assumptions relating to treatment effectiveness Final outcomes not considered Inappropriate distributions considered in PSA

Study	Briggs et al., 2006
Sponsorship	GlaxoSmithKline
Country	UK
Perspective	UK National Health Service perspective
Study type	CUA
Comparators	ICS+LABA (salmeterol ≤50 µg /fluticasone propionate ≤500 µg twice a day) ICS(fluticasone propionate ≤500 µg twice a day)
ICS dosage	fluticasone propionate: ≤500 µg twice a day (low-medium)
Populations	Patients with uncontrolled asthma categorized by (based on 6 months prior to screening entry for study): Stratum 1 – previously ICS-free Stratum 2 – low dose ICS users (≤2500 µg of beclomethasone dipropionate or equivalent) Stratum 3 – moderate ICS dose users(>500 µg to 1000 µg of beclomethasone dipropionate or equivalent) Between the age of 20 and 80 years of age
Time horizon	1 year
Type of model	Trial based model
Cycle length	N/A
Efficacy inputs	Successfully controlled week QALY
Adverse events	Not included
Utilities	AQLQ mapped to utility score
Discounting	N/A
Outcomes	Incremental cost per QALY gained
Results	For Stratum 1, the incremental cost utility ratio for ICS+LABA versus ICS was £13,700 per QALY For Stratum 2, the incremental cost utility ratio for ICS+LABA versus ICS was £11,000 per QALY For Stratum 3, the incremental cost utility ratio for ICS+LABA versus ICS was £7,600 per QALY
Types of sensitivity analysis	Non-parametric bootstrap 95% upper and lower limits

Study	Briggs et al., 2006
Sensitivity analysis results	Non-parametric bootstrap For Stratum 1, lower 95% limit was £11,000 per QALY and the upper 95% limit was £18,300 per QALY For Stratum 2, lower 95% limit was £8,600 per QALY and the upper 95% limit was £14,600 per QALY For Stratum 3, lower 95% limit was £4,800 per QALY and the upper 95% limit was £10,700 per QALY
Points to consider	Costs £(2009-10) Trial based analysis Effectiveness data from a RCT Utility values derived from AQLQ DSA not conducted

Study	Ericsson et al., 2006
Sponsorship	AstraZeneca
Country	Germany and the Netherlands
Perspective	Health care payer perspective Societal perspective Drug Plan perspective
Study type	CEA
Comparators	ICS+LABA (budesonide 4.5 µg/ formoterol 160 µg twice a day) ICS (fluticasone propionate 250 µg twice a day)
ICS dosage	fluticasone propionate: 250 µg twice a day (low)
Populations	Patients with moderate asthma receiving ICS Age 18 and older
Time horizon	12 weeks
Type of model	Trial based analysis
Cycle length	N/A
Efficacy inputs	Number of episode-free days
Adverse events	Not included
Utilities	N/A
Discounting	N/A
Outcomes	Mean number of episode-free days Average cost per patient

Study	Ericsson et al., 2006
Results	Mean number of episode-free days was greater for ICS+LABA compared to ICS (48.71 compared with 42.34 episode-free days) Health care Payer Perspective Average cost per patient was less for ICS+LABA compared to ICS (German €131 /Dutch €101 versus €210/€103) Societal Perspective Average cost per patient was less for ICS+LABA compared to ICS (German €165 /Dutch €128 versus €314/€186) Drug Plan Perspective Average cost per patient was less for ICS+LABA compared to ICS (German €114/Dutch €96 versus €154/€61)
Types of sensitivity analysis	Deterministic analysis (scenario) Exclusion of Israeli data
Sensitivity analysis results	Deterministic analysis (scenario) Results were insensitive to the exclusion of Israeli data
Points to consider	Costs € (2000); conversion €= DM 1.95583, = NGL 2.20371) Trial based analysis Effectiveness data derived from a RCT Final outcomes not considered Limited SA conducted; PSA not performed

Study	Jönsson et al., 2004
Sponsorship	None disclosed; author affiliated with AstraZeneca
Country	Sweden
Perspective	Health care payer perspective Societal perspective
Study type	CEA
Comparators	ICS plus LABA (budesonide 100 µg/formoterol 4.5 µg twice a day) ICS plus LABA (budesonide 200 µg/formoterol 4.5 µg twice a day) ICS (budesonide 100 µg twice a day) ICS (budesonide 200 µg twice a day)
ICS dosage	Budesonide: 100 µg twice a day (low), 200 µg twice a day (low)
Populations	Patients with mild to moderate asthma Age 12 and older
Time horizon	1 year
Type of model	Trial based model
Cycle length	N/A

Study	Jönsson et al., 2004
Efficacy inputs	Number of symptom-free days
Adverse events	Not included
Utilities	N/A
Discounting	N/A
Outcomes	Incremental cost per symptom-free day Incremental cost per severe exacerbation per patient
Results	ICS+LABA combinations were more effective, but more costly than ICS therapy alone. ICER for ICS+LABA (budesonide 200 µg plus formoterol 4.5 µg) versus ICS (budesonide 200 µg) was SEK 21 per symptom-free day ICERs for ICS+LABA (budesonide 200 µg/formoterol 4.5 µg) compared to ICS (budesonide 100 µg) were not reported
Types of sensitivity analysis	Deterministic analysis (scenario) Unit costs from the UK Unit costs from Spain
Sensitivity analysis results	Deterministic analysis (scenario) Results insensitive to scenarios using unit costs from the UK and Spain
Points to consider	Costs SEK (1999) Trial based analysis Effectiveness data from a RCT Final outcomes not considered ICERs not reported for ICS+LABA (budesonide 200 µg/formoterol 4.5 µg) compared to ICS (budesonide 100 µg) PSA not conducted

Study	Price and Briggs, 2002
Sponsorship	GlaxoSmithKline
Country	UK
Perspective	Health care system perspective
Study type	CEA CUA (retrospective modelling without direct utility measures)
Comparators	ICS+LABA (salmeterol 50 µg/fluticasone propionate 100 µg twice a day) ICS (fluticasone propionate 100 µg twice a day)
ICS dosage	fluticasone propionate: 100 µg twice a day(low)
Populations	Patients with asthma with FEV_1 of 40% to 85% and receiving ICS or LABA Aged 12-70 years
Time horizon	12 weeks

Study	Price and Briggs, 2002
Type of model	Markov model
Cycle length	1 week
Efficacy inputs	Successfully controlled weeks QALY
Adverse events	Withdrawal due to adverse events accounted for in treatment failure health state
Utilities	Assumed utility values from a published utilities study (severe exacerbation, mild exacerbation, and current health status) corresponded with into the health states within the model (hospital managed exacerbation, primary care–managed exacerbation, and suboptimal control health state)
Discounting	N/A
Outcomes	Incremental cost per successfully controlled week Incremental cost per QALY gained
Results	The incremental cost-effectiveness ratio for ICS+LABA compared to ICS was £20.83 per successfully controlled week The incremental cost utility ratio for ICS+LABA compared to ICS was £1357 per QALY
Types of sensitivity analysis	Probabilistic analysis (Monte Carlo simulation) Transition probabilities (Dirichlet distribution) Costs (normal distribution)
Sensitivity analysis results	Probabilistic analysis (Monte Carlo simulation) At a willingness to pay of £45 per successfully controlled week, ICS+LABA has the greatest probability of being cost effective
Points to consider	Costs £(2000) Effectiveness data derived from a RCT Withdrawal due to adverse events accounted for in treatment failure health state DSA not conducted PSA considered uncertainty around transition probabilities and costs Assumed utility values from a published utilities study corresponded with into the health states within the model

Study	Andersson et al., 2001
Sponsorship	AstraZeneca
Country	UK, Sweden, Spain
Perspective	Health care system perspective Societal perspective
Study type	CCA CEA

Study	Andersson et al., 2001
Comparators	ICS+LABA (budesonide 200 µg + formoterol 24 µg) ICS+LABA (budesonide 800 µg + formoterol 24 µg) ICS (budesonide 200 µg daily) ICS (budesonide 800 µg daily)
ICS dosage	Budesonide: 200 µg daily (low), 800 µg daily (medium)
Populations	Patients with moderate asthma receiving less than 1600 µg of budesonide Aged 18-70 years
Time horizon	1 year
Type of model	Decision analytic model
Cycle length	N/A
Efficacy inputs	Number of mild exacerbations Number of severe exacerbations Number of symptom-free days Number of episode-free days
Adverse events	Included in episode-free days; however, costs associated with adverse events not specified
Utilities	N/A
Discounting	N/A
Outcomes	Costs (indirect, direct, and total costs) Outcomes (Number of mild exacerbations, severe exacerbations, symptom-free days, and episode-free days) Incremental cost per symptom-free days gained

Study	Andersson et al., 2001
Results	Costs Overall, indirect and direct costs for mild exacerbations were less than for severe exacerbations In the UK, directs associated with ICS+LABA were greater than ICS alone In Sweden, directs associated with were ICS +LABA less than ICS alone In Spain, directs associated with ICS+LABA (budesonide 200 µg + formoterol 24 µg) were less than ICS alone(budesonide 200 µg) and directs associated with ICS+LABA (budesonide 800 µg + formoterol 24 µg) were greater than ICS alone(budesonide 800 µg) Outcomes Overall, there was a gain from adding LABA to ICS in terms of number of mild exacerbations, severe exacerbations, symptom-free days, and episode-free days ICERS (from Health care system perspective) In the UK, ICER for ICS+LABA (budesonide 200 µg + formoterol 24 µg) versus ICS (budesonide 200 µg) was €4.67 per symptom-free day. The incremental cost effective ratio for ICS+LABA (budesonide 800 µg + formoterol 24 µg) versus ICS (budesonide 800 µg) was €6.60 per symptom-free day In Sweden, ICS+LABA (budesonide 200 µg + formoterol 24 µg) dominated ICS (budesonide 200 µg). ICS+LABA (budesonide 800 µg + formoterol 24 µg) also dominated ICS (budesonide 800 µg) In Spain, ICER for ICS+LABA (budesonide 200 µg + formoterol 24 µg) dominated ICS (budesonide 200 µg), while the incremental cost effective ratio for ICS+LABA (budesonide 800 µg + formoterol 24 µg) versus ICS (budesonide 800 µg) was €2.51 per symptom-free day
Types of sensitivity analysis	Deterministic analysis (one-way) Societal perspective – indirect costs Deterministic analysis (threshold analysis) Cost of exacerbation
Sensitivity analysis results	Deterministic analysis (one-way) Totals costs were sensitive to the addition of indirect costs Deterministic analysis (threshold analysis) In the UK, a 69% and 135% increase in the costs of exacerbations is needed to recover the costs of adding LABA to ICS (for budesonide 200 µg + formoterol 24 µg and budesonide 800 µg + formoterol 24 µg respectively) In contrast, a 58% and 41% reduction in the costs of exacerbations is needed to negate cost savings in Sweden Similarly, a 68% and 31% reduction in the costs of exacerbations is needed to negate cost savings in Spain

Study	Andersson et al., 2001
Points to consider	Costs € (1999) Decision analytic model Effectiveness data derived from a RCT Expert opinion consults for resource use Final outcomes not considered PSA not conducted

Study	Lundbäck et al., 2000
Sponsorship	None disclosed; authors affiliated with GlaxoSmithKline (formerly known as Glaxo Wellcome)
Country	Sweden
Perspective	Health care system perspective
Study type	CEA
Comparators	ICS+LABA (salmeterol 50 µg/ fluticasone propionate 250 µg twice a day) ICS(budesonide 800 µg twice a day)
ICS dosage	Budesonide: 800 µg twice a day (high)
Populations	Adolescents and adults with moderate to severe asthma receiving between 800 and 1200 µg of budesonide Aged 12 and older
Time horizon	24 weeks
Type of model	Trial based model
Cycle length	N/A
Efficacy inputs	Successfully treated weeks Episode-free days Symptom-free days
Adverse events	Included in episode-free days; however, costs associated with adverse events not specified
Utilities	N/A
Discounting	N/A
Outcomes	Incremental cost per successfully treated week Incremental cost per episode-free day Incremental cost per symptom-free day
Results	ICER for ICS+LABA versus ICS was SEK 31.6 per successfully treated week ICER for ICS+LABA versus ICS was SEK 51.1 per episode-free day ICER for ICS+LABA versus ICS was SEK 9.2 per symptom-free day

Study	Lundbäck et al., 2000
Types of sensitivity analysis	Deterministic analysis (one-way) Improvement in morning peak expiratory flow Deterministic analysis (best/worst case scenarios) All withdrawn patients were symptom- and episode-free from the time of withdrawal All withdrawn patients were symptomatic and not episode-free from the time of withdrawal
Sensitivity analysis results	Deterministic analysis (one-way) Results insensitive to improvement in morning peak expiratory flow Deterministic analysis (best/worst case scenarios) Results insensitive to best and worst case scenarios
Points to consider	Costs SEK (1998) Effectiveness data derived from a RCT Trial based analysis PSA not conducted Final outcomes not considered

Study	Palmqvist et al., 1999
Sponsorship	None disclosed; authors affiliated with GlaxoSmithKline (formerly known as Glaxo Wellcome)
Country	Sweden
Perspective	Health care system perspective
Study type	CEA
Comparators	ICS plus LABA (salmeterol 50 µg/ fluticasone propionate 250 µg twice a day) ICS (fluticasone propionate 250 µg twice a day)
ICS dosage	fluticasone propionate: 250 µg twice a day (low)
Populations	Adolescents and adults with moderate to severe asthma Age not specified
Time horizon	12 weeks
Type of model	Trial based model
Cycle length	N/A
Efficacy inputs	Mean proportion of successfully treated weeks Mean proportion of episode-free days Mean proportion of symptom-free days
Adverse events	Included in episode-free days; however, costs associated with adverse events not specified
Utilities	N/A
Discounting	N/A

Study	Palmqvist et al., 1999
Outcomes	Incremental cost per successfully treated week Incremental cost per episode-free day Incremental cost per symptom-free day
Results	ICERs for ICS+LABA versus ICS were SEK 12.6 per successfully treated week, SEK 3.9 per episode-free day, and SEK 3.9 per symptom-free day
Types of sensitivity analysis	Deterministic sensitivity analysis (one way) Improvement in morning peak expiratory flow Deterministic sensitivity analysis (best/worst case scenarios) All days following withdrawal were symptomatic or not episode-free All days following withdrawal were was episode- or symptom-free
Sensitivity analysis results	Deterministic sensitivity analysis (one way) Results were insensitive to changes to improvements in morning peak expiratory flow Deterministic sensitivity analysis (best/worst case scenarios) Results were insensitive to best/worst case scenarios; as results continued to favour ICS+LABA
Points to consider	Costs SEK (Year not disclosed) Trial based analysis Effectiveness data from a RCT Final outcomes not considered PSA not conducted

Study	Pieters et al.,1999
Sponsorship	None disclosed; authors affiliated with GlaxoSmithKline (formerly known as Glaxo Wellcome)
Country	Sweden
Perspective	Health care system perspective
Study type	CEA
Comparators	ICS plus LABA (fluticasone propionate 500 µg/ salmeterol 50 µg twice a day) ICS (fluticasone propionate 500 µg twice a day)
ICS dosage	fluticasone propionate: 500 µg twice a day (medium)
Populations	Adolescent and adult patients with corticosteroid-dependent asthma Age not specified
Time horizon	12 weeks
Type of model	Trial based model
Cycle length	N/A

Study	Pieters et al.,1999
Efficacy inputs	Mean proportion of successfully treated weeks Mean proportion of episode-free days Mean proportion of symptom-free days
Adverse events	Included in episode-free days; however, costs associated with adverse events not specified
Utilities	N/A
Discounting	N/A
Outcomes	Incremental cost per successfully treated week Incremental cost per episode-free day Incremental cost per symptom-free day
Results	The incremental cost-effectiveness ratios for ICS+LABA versus ICS were SEK 192.1 per successfully treated week, SEK 66.8 per episode-free day, and SEK 120.0 per symptom-free day
Types of sensitivity analysis	Deterministic sensitivity analysis (one way) Improvement in morning peak expiratory flow Deterministic sensitivity analysis (best/worst case scenarios) All days following withdrawal were symptomatic or not episode-free All days following withdrawal were was episode- or symptom-free
Sensitivity analysis results	Deterministic sensitivity analysis (one way) Results were insensitive to changes to improvements in morning peak expiratory flow Deterministic sensitivity analysis (best/worst case scenarios) Results were insensitive to best/worst case scenarios; as results continued to favour ICS+LABA
Points to consider	Costs SEK (Year not disclosed) Trial based analysis Effectiveness data from a RCT Final outcomes not considered

Study	Johansson et al., 1999
Sponsorship	None disclosed; authors affiliated with GlaxoSmithKline (formerly known as Glaxo Wellcome)
Country	Sweden
Perspective	Health care system perspective
Study type	CEA
Comparators	ICS+LABA (salmeterol 50 µg/ fluticasone propionate 100 µg twice a day) ICS(fluticasone propionate 100 µg twice a day)
ICS dosage	fluticasone propionate: 100 µg twice a day (low)

Study	Johansson et al., 1999
Populations	Adolescent and adult patients with asthma Age 12 and older
Time horizon	12 weeks
Type of model	Trial based model
Cycle length	N/A
Efficacy inputs	Mean proportion of successfully treated week Mean proportion of symptom-free days Mean proportion of episode-free days
Adverse events	Included in episode-free days; however, costs associated with adverse events not specified
Utilities	N/A
Discounting	N/A
Outcomes	Incremental cost per successfully treated week Incremental cost per symptom-free days Incremental cost per episode-free days
Results	The incremental cost per successfully treated week for ICS+LABA versus ICS was 133.4 SEK per successfully treated week The incremental cost per symptom-free days for ICS+LABA versus ICS was 44.5 SEK per symptom-free days The incremental cost per episode-free days for ICS+LABA versus ICS was 46.9 SEK per episode-free days
Types of sensitivity analysis	Deterministic analysis (best/worst case scenarios) All days following withdrawal were symptomatic or not episode-free All days following withdrawal were was episode- or symptom-free Deterministic analysis (one-way) Improvement in morning peak expiratory flow
Sensitivity analysis results	Deterministic sensitivity analysis (best/worst case scenarios) Results were insensitive to best/worst case scenarios; as results continued to favour ICS+LABA Deterministic analysis (one-way) Results were insensitive to changes in improvements in morning peak expiratory flow
Points to consider	Costs SEK (year not disclosed) Trial based analysis Effectiveness data from a RCT Final outcomes not considered PSA not conducted

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 asthma compared to ICS alone?

Study Objective

The objective of the primary economic evaluation was to assess the cost-effectiveness of alternative strategies for incorporating LABA plus ICS maintenance therapy into the management of asthma patients. Specifically, the study is designed to determine at what stage the incorporation of LABA plus ICS maintenance therapy into the management of patients would be cost effective

Economic Evaluation

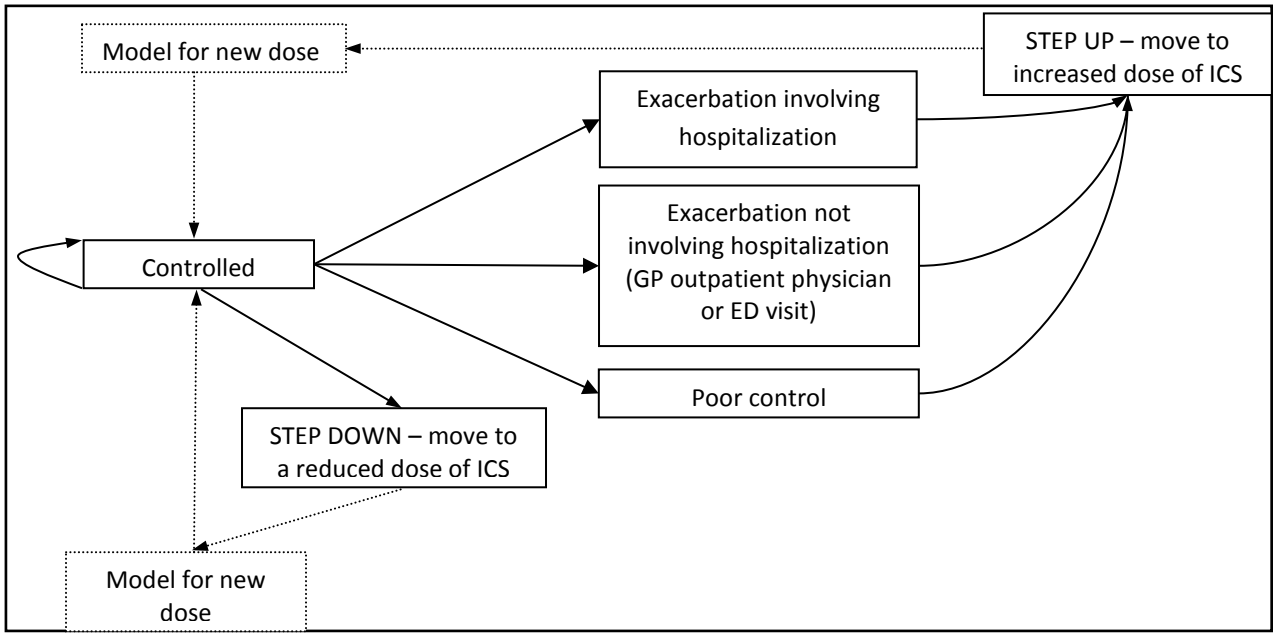
Model Structure

Analysis consisted of a cost-utility analysis (CUA) following the CADTH guidelines for economic evaluations.[25]

The analysis was conducted from the perspective of a provincial ministry of health. Effectiveness was assessed in the form of QALYs. Primary analysis was conducted for a one year time horizon with secondary analysis with a time horizon of 12 weeks. Given the limited time horizon for both the primary and secondary analyses, no discounting was required.

A Markov cohort model was developed using Microsoft Excel™ to predict the outcomes of each of the pharmaceutical management strategies.[206] The Markov model used a cycle length of two weeks to reflect the time for recovery from exacerbations. Within the Markov model (Figure 1), the patient cohort transitions every two weeks with respect to their prescribed drug therapy (same dose, reduced dose (step down) and increased dose of ICS (step up)) and the incidence of exacerbations (GP managed, outpatient managed, Emergency Department [ED] visits, and hospitalizations). For each new dose, the model structure is replicated but new transition probabilities and drug costs will apply.

Figure 1 Schematic of Markov Model



Treatment Comparators

Four specific strategies are considered which relate to three distinct decision points where the option of ICS+LABA combination therapy can be adopted.

At model entry, the study cohort was assumed to be ICS naïve and patients could commence with low dose ICS or a combination product of low dose ICS+LABA.

For the latter strategy, if patients are uncontrolled on low dose ICS+LABA they would move to moderate dose ICS+LABA and then to high dose ICS+LABA. This is referred to as Strategy 1

For patients commencing therapy with low dose ICS, the next decision point is if they experience a lack of control or exacerbation at this dose. At this point there are two options: increase their dose of ICS to moderate dose ICS or add a LABA – low dose ICS+LABA. For the latter strategy, if patients are uncontrolled on low dose ICS+LABA they would move to moderate dose ICS+LABA and then to high dose ICS+LABA. This is referred to as Strategy 2.

For patients moving to moderate dose ICS after lack of control on low dose ICS, the next decision point is if they experience a lack of control or exacerbation at this dose. At this point there are again two options: increase their dose of ICS to high dose ICS or add a LABA – moderate dose ICS+LABA. For the latter strategy, if patients are uncontrolled on moderate dose ICS+LABA they would move to high dose ICS+LABA. This is referred to as Strategy 3. For those who increase their dose to high dose ICS, if they experience a lack of control they would move to high dose ICS+LABA (Strategy 4).

Thus, the strategies relate specifically to the time point at which ICS+LABA combination products are

adopted: for patients who are naïve to ICS (Strategy 1), after lack of control on low dose ICS (Strategy 2), after lack of control on moderate dose ICS (Strategy 3) and after lack of control on high dose ICS (Strategy 4).

The dose of ICS was based on current Canadian guidelines for the management of asthma.[207] Naïve patients were assumed to start on the same dose of ICS whether they begin on LABA/ICS combination therapy or ICS monotherapy. For uncontrolled patients, it was assumed that patients either have a LABA added to their current dose or increase their dose of ICS as a monotherapy.

Given the paucity of data and lack of differences between LABA/ICS combination agents, analysis was conducted for LABA/ICS as a whole, rather than specifically for each type of combination therapy compared to the use of ICS monotherapy. Costs of both LABA/ICS and ICS were derived based on a weighted average of current use specific to ICS dosage as identified by the data utilized within the budget impact analysis.

Data Inputs

Data Values

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

Transition probabilities

For each treatment within each strategy, the following probabilities are required:

- the probability of step up in therapy,
- the probability of step down in therapy,
- the probability of a medically managed exacerbation,
- the probability that a medically managed exacerbation is managed by a GP visit, an outpatient specialist visit, an ED visit or a hospitalization.

The probability of a step up in therapy was assumed to be due to lack of control which was measured via a combination of withdrawal rates, as implemented within previous asthma models, and medically managed exacerbations. [8,159]

First, the probability of withdrawal for different dosages of ICS monotherapy were calibrated to a two week period and then combined as a weighted sum to get a baseline weekly rate. The relative risk of withdrawal on combination therapy versus monotherapy was obtained from a previous meta-analysis.[159] Both the probabilities of withdrawal and the relative risk of withdrawal on combination therapy came from a previous Canadian HTA.[159]

The probability of an exacerbation for both monotherapy and combination therapy were taken directly from the RCTs contained within the companion systematic review. First, exacerbations for the ICS monotherapy arms were transformed to a two weekly exacerbation probability and then combined as a

weighted sum to estimate a baseline probability. Secondly, estimates of the effectiveness of LABA+ICS combination products in terms of the relative risk of exacerbation came from random effects meta-analysis using data from studies directly comparing the relevant LABA+ICA combination products to ICS monotherapies. The probability of exacerbation for combination therapy was the product of the probability for the pertinent monotherapy and the relative risk.

Although the definition of exacerbation differed among studies, we adopted the same definition of moderate to severe exacerbations from the companion systematic review (e.g., worsening of asthma symptoms that may require hospitalization, emergency department visits, treatment with oral steroids and/or antibiotics, use of rescue medication, unscheduled visits)

The proportions of exacerbations which required a family physician visit, outpatient specialist visit, ED visit or hospital stay were derived from national surveillance data from the Centre for Disease Control.[208] Sensitivity analysis adopted the distribution based on a previous Canadian HTA.[159] As sufficient data were not available from the published studies, we assumed that therapy impacts only the rate of exacerbation, but not the type of exacerbations. The direction of bias with this assumption is unknown but the impact was tested by sensitivity analysis.

In the baseline analysis, we assumed that no exacerbations are self-managed. This can be seen as an assumption biased in favour of the more active therapies and was subject to sensitivity analysis.

The probability of a step down in therapy was not available from the RCTs. Thus, we adopted the same rate for step down as contained in a previous NHS HTA[27] where the rate was assumed constant for all treatment options. However, for patients on a low dose of ICS we assumed no probability of step down. Sensitivity analysis was conducted whereby the probability of step down was doubled for patients on combination therapy.

Resource use and costs

Analysis required estimates of the two week costs of drug therapy and the costs associated with the management of exacerbations. All costs were estimated in 2014 Canadian dollars with adjustments based on the Bank of Canada Inflation calculator.[209] Two week costs of drug therapy were estimated as the weighted average of different combination therapies and ICS monotherapy for low, medium and high doses of ICS. We derived weights based on current usage as identified in the data used in the companion budget impact analysis. For each alternative treatment, we calculated the prescription costs based on data from the Ontario Drug formulary including an 8% pharmacist's mark up and a $8.83 dispensing fee.[210]

Costs of exacerbations were obtained from appropriate Canadian sources. The costs of a GP managed exacerbation and an outpatient specialist visit were derived from the Ontario Schedule of Fees and Benefits. [211] The cost of an ED managed exacerbation was assumed to include ED physician fees derived from the Ontario Schedule of Fees and Benefits and hospital costs obtained from the Province of Alberta. [211,212] The costs of hospitalizations were derived from the Ontario Case Costing Initiative data.[213]

Utilities

Utility values were derived from a 2006 study by Lloyd and colleagues of 112 patients with asthma who completed the EQ-5D.[214] Utility values were obtained for asthma without an exacerbation, exacerbation without hospitalization and exacerbation with hospitalization.

In the base case we assumed there were no treatment-specific effects on utility values – rather utilities would differ by treatment solely based on the different rates of exacerbations. In a previous asthma study, Paltiel and colleagues had explored the impact of assuming lower utility values with ICS therapy due to the increased side effects such as dysphonia and thrush. In the absence of data relating to this, they assumed that utility values would be reduced by up to 3% for patients on ICS. [215] To similarly explore the impact of higher doses of ICS, although evidence to support this is lacking, we conduct an exploratory analysis in which we assumed a 1% reduction in utility values for patients on low dose ICS, a 2% reduction associated with moderate dose ICS and 3% with high dose ICS. This sensitivity analysis would address the implications of any potential utility gain from adding LABA rather than increasing the dose of ICS.

Cost-effectiveness

A cost-utility analysis was conducted whereby, costs and effects as measured by life years and quality adjusted life years (QALYs) gained associated with the different treatment strategies are estimated via the model. Base analysis was conducted through a deterministic analysis whereby point estimates for each parameter were entered into the model. This provides an estimate of the costs, QALYs, and effectiveness for each alternative, and allows estimation of incremental cost-effectiveness ratios.

Deterministic Sensitivity Analyses

Deterministic sensitivity analysis was conducted to assess the robustness of the study's results to changing assumptions within the model.[216] Specific analyses conducted were:

- analysis for 12 weeks rather than 52 weeks
- assuming different rates of exacerbations were managed through self-care (25%, 50%, 75% - base case = 0%)
- assuming LABA/ICS reduces the proportion of exacerbations requiring medical management (25%, 50%, 75% - base case = 100%)
- assuming the proportion of exacerbations managed by GP, specialists, ED or hospitalization as per a previous Canadian HTA report[159]
- assuming no step down on ICS monotherapy
- using odds ratio for exacerbations based on the network meta-analysis within the companion systematic review
- the probability of step down was doubled for patients on combination therapy
- assuming reduction in utility values for higher doses of ICS

In addition, we undertook a threshold analysis related to the additional SABA use for patients on ICS

monotherapy. Analysis focused on identifying the increase in weekly SABA use that would have to be associated with ICS monotherapy for ICURs to be lower than $50000.

Probabilistic Sensitivity Analyses

In addition, probabilistic analysis was conducted using a Monte Carlo simulation (MCS).[217] For the MCS, probability distributions related to transition probabilities, relative risks, costs, and utilities were incorporated into the analysis. Estimates of incremental costs and QALYs were obtained by re-running the model employing values from the related probability distributions. In this study, 5000 replications were conducted; i.e. a set of 5000 outcome estimates was obtained. Cost-effectiveness acceptability curves (CEACs) were derived for each patient population which present the probability that each therapeutic strategy is optimal given different values of willingness to pay for an additional QALY.[218]

Findings

Base Case

The detailed results of the CUA are provided in Table 1. The earlier LABAs are introduced, the greater the QALYs. However, the incremental QALY gain for strategies involving early introduction of LABA is small for all comparisons at 12 weeks and one year. Total costs are higher the earlier LABA is introduced for all four strategies.

The incremental cost-utility ratio (ICUR) falls the later a LABA is introduced into therapy for analysis at 1 year. The incremental cost per QALY gained from initiating treatment with a LABA plus ICS rather than introducing LABA after lack of control on low dose ICS monotherapy is $1.27 million. The incremental cost per QALY gained from introducing LABA after lack of control on low dose ICS monotherapy compared to introducing it after lack of control on medium dose ICS monotherapy is $410,963. Finally, the incremental cost per QALY gained from introducing LABA after lack of control on moderate dose ICS monotherapy compared to introducing it after lack of control on high dose ICS monotherapy is $332,684. The incremental cost per QALY gained is similar for analysis at 12 weeks and one year.

Table 1 Cost Utility Analysis of Different Strategies for the Introduction of LABA to ICS

	12 weeks Total QALYs	Total Costs	Sequential ICUR	52 weeks Total QALYs	Total Costs	Sequential ICUR
Introduction of LABA after uncontrolled on high dose ICS (Strategy 4)	0.2037	$97.90		0.8829	$517.41	
Introduction of LABA after uncontrolled on medium dose ICS (Strategy 3)	0.2037	$98.13	$333,917	0.8829	$534.45	$332,684
Introduction of LABA after uncontrolled on low dose ICS (Strategy 2)	0.2037	$106.96	$435,050	0.8832	$656.75	$410,963
Introduction of LABA/ICS to patients naïve to ICS (Strategy 1)	0.2039	$271.28	$735,961	0.8837	$1288.25	$1,267,586

The detailed results of the secondary CEA are presented in Table 2. Similar findings to the CUA were found with respect to the decrease in exacerbations the earlier LABAs were introduced but with a corresponding decline in incremental cost-effectiveness ratio the later LABA is introduced to therapy.

The incremental cost per Exacerbation avoided from initiating treatment with a LABA plus ICS rather than introducing LABA after lack of control on low dose ICS monotherapy is $16,040. The incremental cost per exacerbation avoided from introducing LABA after lack of control on low dose ICS monotherapy compared to introducing it after lack of control on medium dose ICS monotherapy is $5,200. Finally, the incremental cost per exacerbation avoided from introducing LABA after lack of control on moderate dose ICS monotherapy compared to introducing it after lack of control on high dose ICS monotherapy is $4,210. The incremental cost per exacerbation avoided is similar for analysis at 12 weeks and one year.

Table 2 Cost-effectiveness Analysis of Different Strategies for the Introduction of LABA to ICS

	Number of Exacerbations	Total Costs	Sequential Incremental Cost per Exacerbation Avoided
Introduction of LABA after uncontrolled on high dose ICS (Strategy 4)	0.56255	$517.41	
Introduction of LABA after uncontrolled on medium dose ICS (Strategy 3)	0.55850	$534.45	$4,210
Introduction of LABA after uncontrolled on low dose ICS (Strategy 2)	0.53498	$656.75	$5,200
Introduction of LABA/ICS to patients naïve to ICS (Strategy 1)	0.49561	$1,288.25	$16,040

Analysis for 1 year time horizon

Deterministic Sensitivity Analysis

The detailed results of the univariate sensitivity analysis are provided in **Table 3**. In the majority of instances, these results were insensitive to changes in assumptions as the ICURs do not differ greatly from the base-case analysis. The two scenarios in which the ICURs did differ markedly from the base case were for the incorporation of the odds ratios from the current meta-analysis and the analysis incorporating a disutility associated with increasing ICS dose.

When the odds ratios from the current meta-analysis were incorporated, the ICURs were lower than those within the base case analysis; however, there were no comparisons in which the ICUR for earlier introduction of LABA therapy was lower than $100,000 per QALY.

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

Within the exploratory analysis which incorporated an increasing disutility associated with increasing ICS dosages, the introduction of LABA combination therapy in patients uncontrolled on medium dose ICS would be considered cost effective relative to delaying introduction until after an increase to high dose ICS. The ICUR for introduction of LABA if uncontrolled on medium dose ICS versus if uncontrolled on high dose ICS is $6,373 per QALY. The two alternative strategies involving initiating LABA combination therapy in patient's naïve to ICS or in those uncontrolled on low dose ICS remain not cost effective.

The threshold analysis relating to SABA use examined the required incremental weekly SABA use on ICS monotherapy which would lead to the incremental cost per QALY gained of $50,000 based on a 52-week time horizon. For naïve patients, the incremental use of SABA on ICS monotherapy would have to be 164 additional puffs per week. For patients uncontrolled on low dose ICS, the incremental use of SABA on ICS monotherapy would have to be 29 additional puffs per week. For patients uncontrolled on medium dose ICS, the incremental use of SABA on ICS monotherapy would have to be 4 additional puffs per week.

Table 3 Results of Deterministic Sensitivity Analysis

Scenario	Incremental Cost per QALY gained (52 weeks)		
	Strategy 4 vs Strategy 3	Strategy 3 vs Strategy 2	Strategy 2 vs Strategy 1
Base Case	$332,684	$410,963	$1,267,586
No ICS step down	$333,202	$410,424	$1,298,027
25% of exacerbations self-managed	$339,568	$418,386	$1,280,904
50% of exacerbations self-managed	$346,548	$425,912	$1,294,406
75% of exacerbations self-managed	$353,625	$433,543	$1,308,097
LABA/ICS reduce medically managed exacerbations by 25%	$285,877	$381,675	$1,152,054
LABA/ICS reduce medically managed exacerbations by 50%	$243,255	$353,935	$1,049,539
LABA/ICS reduce medically managed exacerbations by 75%	$204,280	$327,624	$957,958
Alternate distributions for exacerbation management	$353,135	$433,314	$1,310,723
Odds ratios derived from meta-analysis	$122,901	$113,236	$183,437
Doubling of the probability of step down on combination therapy	$790,816	$435,485	$309,612
Disutility associated with increasing ICS dose	$6,373	$322,669	Dominated by strategy 2 and 3

Strategy 4: Introduction of LABA after uncontrolled on high dose ICS
Strategy 3: Introduction of LABA after uncontrolled on medium dose ICS
Strategy 2: Introduction of LABA after uncontrolled on low dose ICS
Strategy 1: Introduction of LABA/ICS to patients naïve to ICS

Probabilistic Sensitivity Analysis

Within the probabilistic analysis, the incremental cost per QALY gained from introducing LABA increased in all situations Table 4. The ICURs based on the probabilistic analysis did not differ significantly from those estimated within the base case analysis.

The probabilities that each of the four treatment strategies is optimal based on alternative threshold values of a QALY are provided in Figure 1. For threshold values for a QALY up to $100,000 the probability that strategy 4 (adding LABA to patients uncontrolled on high dose ICS) is optimal is 100%. For all threshold values between $100,000 and $200,000, the probability that either Strategy 1 (adding LABA to treatment naïve patients), Strategy 2 (adding LABA to patients uncontrolled on low dose ICS), or Strategy 3 (adding LABA to patients uncontrolled on medium dose ICS) are optimum is never greater than 10%.

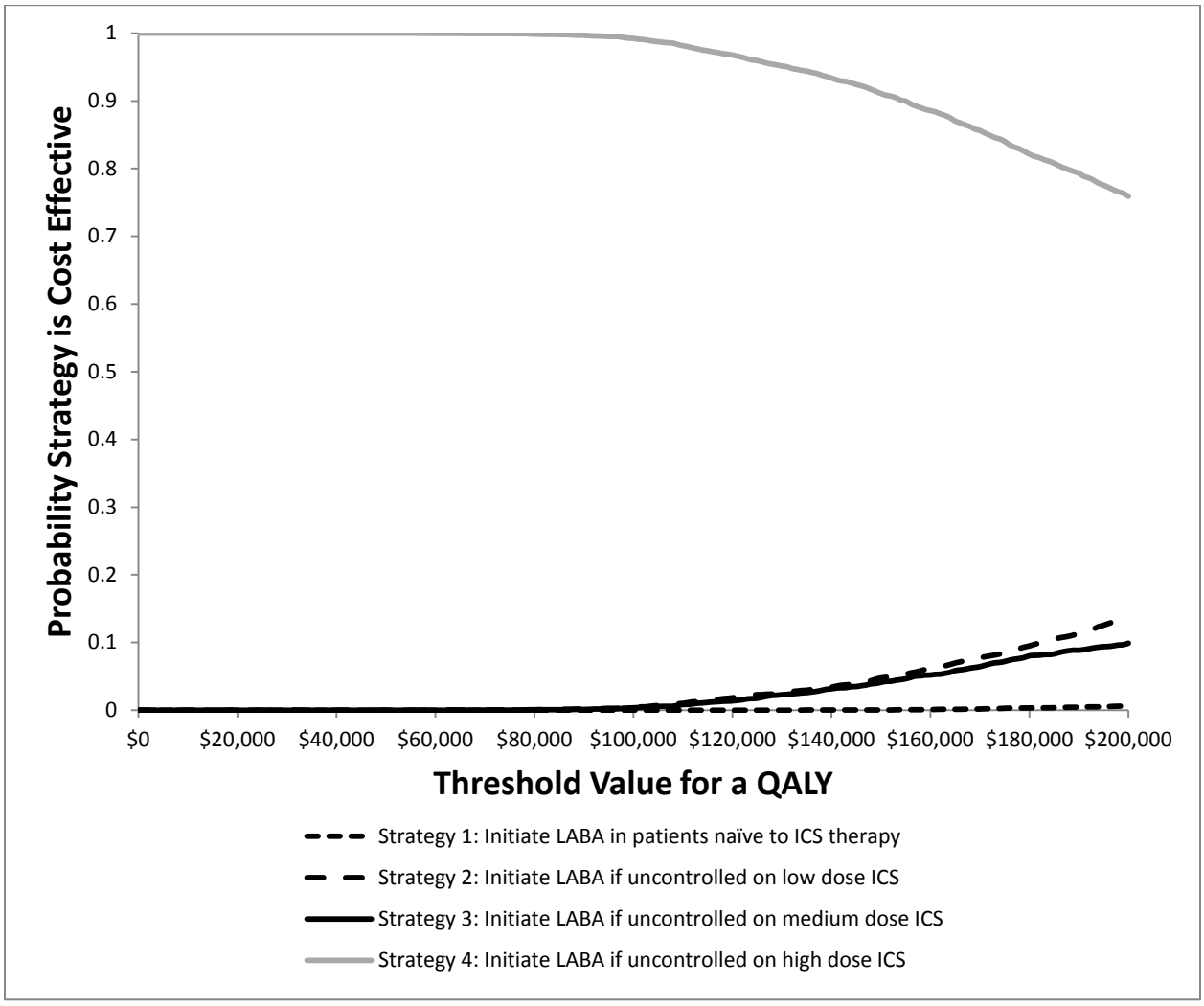
Table 4 Results of Probabilistic Sensitivity Analysis

	Costs	QALYs	Sequential ICUR
Introduction of LABA after uncontrolled on high dose ICS (Strategy 4)	$517.54 (452.91, 596.20)	0.88267 (0.847, 0.911)	
Introduction of LABA after uncontrolled on medium dose ICS (Strategy 3)	$534.85 (464.69, 618.20)	0.77272 (0.847, 0.911)	$341,110[3]
Introduction of LABA after uncontrolled on low dose ICS (Strategy 2)	$657.82 (563.60, 761.90)	0.88299 (0.847, 0.911)	$451,720[2]
Introduction of LABA/ICS to patients naïve to ICS (Strategy 1)	$1293.89 (1203.02, 1406.06)	0.88345 (0.847, 0.912)	$1,376,995[1]

Analysis is for 1 year time horizon.

Figures in parenthesis are 95% credible intervals

Figure 2 Cost-effectiveness Acceptability Curve



Conclusions

The economic analysis found that the later LABA was introduced into therapy the more cost effective the treatment strategy became. When compared with only adding a LABA in patients who remained uncontrolled on high dose inhaled corticosteroids, none of the strategies involving earlier introduction of combination therapy at lower doses of ICS would be considered cost-effective by conventional definitions and the ICUR exceeded $300,000 per QALY. Thus, the optimum strategy considered was introducing LABA to patients when they were uncontrolled at high doses of ICS. Exploratory analysis showed that if the combination of LABA and ICS were shown to be corticosteroid sparing, and increasing doses of ICS were associated with reduced utility, earlier introduction of combination therapy in patients uncontrolled on medium dose ICS would be cost effective. The data to support these assumptions, however, is currently lacking.

In conclusion, the introduction of LABA before patients have tried high dose ICS monotherapy does not appear justified based on the criteria of cost-effectiveness.

Appendix B1: Data Estimates

Table 5 Data Estimates

INPUT	DATA	VALUE	DISTRIBUTION	SOURCE
Probabilities and relative risks				
Probability of withdrawal (weekly)	low dose ICS	0.005	Beta (16.2,3321.8)	
	moderate dose ICS	0.006	Beta (22.6,4019.4)	
	high dose ICS	0.006	Beta (7.4,1144.6)	
Proportion of exacerbation (weekly)	low dose ICS	0.011	Beta (26.5,2312.5)	
	moderate dose ICS	0.01	Beta (25.5,2649.5)	
	high dose ICS	0.012	Beta (14.9,1220.1)	
RR of withdrawal	naïve - ICS/LABA low dose vs ICS low dose	1.027	Lognormal (0.519,2.031)	
	ICS/LABA low dose vs ICS med dose	0.936	Lognormal (0.5,1.7)	
	ICS/LABA med dose vs ICS high dose	0.872	Lognormal (0.3,2.5)	
	ICS/LABA high dose vs ICS high dose	0.842	Lognormal (0.4,1.9)	
RR of exacerbation	naïve - ICS/LABA low dose vs ICS low dose	0.84	Lognormal (0.6,1.3)	
	ICS/LABA low dose vs ICS med dose	0.81	Lognormal (0.5,1.3)	
	ICS/LABA med dose vs ICS high dose	0.87	Lognormal (0.8,1)	
	ICS/LABA high dose vs ICS high dose	0.6	Lognormal (0.5,0.7)	
Probability of stepdown		0.00203	Beta (2.5,1219.6)	
Annual rate of exacerbations (used to derive distribution of exacerbation by type)	Family physician visit	0.394	Beta (21.9,33.6)	
	Outpatient department visit	0.023	Beta (32.3,1371.2)	
	ED	0.071	Beta (95.5,1249.6)	
	Hospitalization	0.019	Beta (88.5,4570.2)	
Utilities				
No exacerbation		0.89	Lognormal (0.89,0.02)	
Exacerbation	Not requiring medical management	0.57	Lognormal (0.57,0.08)	
	GP visit	0.57	Lognormal (0.57,0.08)	
	Outpatient specialist visit	0.57	Lognormal (0.57,0.08)	

INPUT	DATA	VALUE	DISTRIBUTION	SOURCE
	ER visit	0.57	Lognormal (0.57,0.08)	
	Hospitalized	0.33	Lognormal (0.33,0.17)	
Costs				
Two week drug costs	ICS low	$10.45	Fixed	
	ICS medium	$19.03		
	ICS high	$37.95		
	LABA/ICS low	$39.91		
	LABA/ICS medium	$51.74		
	LABA/ICS high	$81.59		
Exacerbation costs	Not requiring medical management	$0.00	Fixed	
	GP visit	$38.35	Fixed	
	Outpatient specialist visit	$157.00	Fixed	
	ER visit	$412.87	Fixed	
	Hospitalized	$3,635.21	Gamma (323.1,10.8)	

Figures in parenthesis are alpha and beta for probabilities and rates, 95% confidence intervals for relative risks, mean and standard errors for utility values and shape and scale parameters for costs.

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 asthma?

Reimbursement Based Economic Assessment

An applied, policy oriented economic model focusing on financial impact was created to facilitate consideration of alternative reimbursement scenarios for asthma therapy. OPDP usage data for asthma therapies (ICS, LABA and LAMA, both as single and combination therapies) from April 2011 to March 2012 and April 2012 to March 2013 was collected and are presented in this report. However, the budget impact analysis used only the most recent year of OPDP usage data (April 2012 to March 2013). Asthma patients aged 12 years and older who were dispensed at least one prescription for asthma therapy (LABA, LAMA, ICS, ICS+LABA) in Ontario were included in the analysis. The model was developed using Microsoft Excel.

First, asthma therapies were defined, as follows:

Table 6 Asthma Therapy Details

ASTHMA 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

ASTHMA THERAPY	DETAILS
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

Second, the assumptions for the budget impact analysis were specified.

Table 7 Budget Impact Analysis – General Assumptions

Assumptions
The scenarios only apply to users of triple therapy combo (ICS+LABA combo plus LAMA), combination therapy (ICS+LABA), single prescription - multiple therapy – ICS+LABA combo plus LAMA, and single prescription – ICS+LABA combo

Afterwards, alternative approaches to reimbursement of asthma therapy were identified. The base case reimbursement scenarios relate to the concept that ICS+LABA combination products are only covered at higher doses of ICS based on the need for trials of ICS at higher doses. The first scenario is that ICS+LABA is covered only after a trial of medium dose ICS – this precludes coverage of combination therapies including low dose ICS+LABA. The second scenario is that ICS+LABA is covered only after a trial of high dose ICS – this precludes coverage of combination therapies including low and medium dose ICS+LABA. Analysis also assessed the impact of patients being moved to higher dose ICS in combination with LABA: e.g. if combination therapies with low dose ICS+LABA are not covered, patients may be moved to a combination of medium dose ICS +LABA when uncontrolled on low dose ICS.

Table 8 Budget Impact Analysis – Reimbursement Scenarios

REIMBURSEMENT SCENARIO	DESCRIPTION
STATUS QUO -	
CURRENT REIMBURSEMENT	• No changes to current reimbursement of asthma therapy
BASE CASE	
STRATEGY #1 -	
COVERAGE OF ICS+LABA ONLY AFTER TRIAL OF MEDIUM DOSE ICS	• Patients uncontrolled on low dose ICS move to medium dose ICS rather than low dose ICS plus LABA
STRATEGY #2 -	
COVERAGE OF ICS+LABA ONLY AFTER TRIAL OF HIGH DOSE ICS	• Same approach as STRATEGY #1 AND • Patients uncontrolled on medium dose ICS move to high dose ICS rather than medium ICS dose plus LABA
SENSITIVITY ANALYSIS	
STRATEGY #1B -	
COVERAGE OF ICS+LABA ONLYAFTER TRIAL OF MEDIUM DOSE ICS	• 50% of patients uncontrolled on low dose ICS move to medium dose ICS while 50% move to medium dose ICS plus LABA without trial of medium dose ICS
STRATEGY #2B -	
COVERAGE OF ICS+LABA ONLY AFTER TRIAL OF HIGH DOSE ICS	• Patients uncontrolled on low dose ICS move to medium dose ICS rather than low dose ICS plus LABA AND • 50% of patients uncontrolled on medium dose ICS move to high dose ICS while 50% move to high dose ICS plus LABA without trial of high dose ICS

For **STRATEGY #1**, to assess the impact we assumed that all current users of triple therapy (ICS+LABA combo + LAMA), combination therapy (ICS+LABA), single prescription ICS+LABA combo + LAMA, and single prescription – ICS+LABA combo who are on a low dose ICS would instead be treated by ICS medium dose.

For **STRATEGY #2,** the same approach as STRATEGY #1 was adopted with the addition that all current users of triple therapy (ICS+LABA combo + LAMA), combination therapy (ICS+LABA), single prescription ICS+LABA combo + LAMA, and single prescription – ICS+LABA combo who are on a medium dose ICS would instead be treated by ICS high dose.

For **STRATEGY #1B**, to assess the impact of physicians prescribing higher dose ICS in combination with LABA as response to the non-funding of combination products incorporating low dose ICS with LABA, we assumed that only 50% current users of triple therapy (ICS+LABA combo + LAMA), combination therapy (ICS+LABA), single prescription ICS+LABA combo + LAMA, and single prescription – ICS+LABA combo who are on a low dose ICS would instead be treated by ICS medium dose whilst 50% would be treated with

combination therapies involving medium dose ICS +LABA..

For **STRATEGY #2B**, we first assumed that all current users of triple therapy (ICS+LABA combo + LAMA), combination therapy (ICS+LABA), single prescription ICS+LABA combo + LAMA, and single prescription – ICS+LABA combo who are on a low dose ICS would instead be treated by ICS medium dose. However, we assumed that only 50% current users of triple therapy (ICS+LABA combo + LAMA), combination therapy (ICS+LABA), single prescription ICS+LABA combo + LAMA, and single prescription – ICS+LABA combo who are on a medium dose ICS would instead be treated by ICS high dose whilst 50% would be treated with combination therapies involving high dose ICS +LABA.

Findings

Current Usage and Expenditure

Table 9 Asthma Therapy Users by Year

	USERS N(%)	
	2011*	**2012^**
Total	183,352(100%)	191,073(100%)
Multiple Prescriptions		
Triple therapy ICS+LABA combo + LAMA	28,345(15%)	29,511(15%)
Triple therapy dual	522(0%)	443(0%)
Combination therapy (ICS+LABA combo)	54,030(29%)	57,604(30%)
Dual therapy ICS + LABA	1,132(1%)	1,006(1%)
Dual therapy ICS + LAMA	3,209(2%)	2,954(2%)
Dual therapy LAMA + LABA	316(0%)	279(0%)
Single therapy ICS	27,881(15%)	28,020(15%)
Single therapy LABA	516(0%)	522(0%)
Single therapy LAMA	7,057(4%)	7,120(4%)
Single Prescription		
Multiple therapy - ICS+LABA combo + LAMA	1,377(1%)	1,611(1%)
Multiple therapy - ICS + LABA + LAMA	10(0%)	5(0%)
Combination therapy (ICS+LABA combo)	28,246(15%)	30,148(16%)
Multiple therapy - ICS + LABA	130(0%)	103(0%)
Multiple therapy - ICS + LAMA	302(0%)	276(0%)
Multiple therapy - LABA + LAMA	10(0%)	18(0%)
Single therapy – ICS	27,378(15%)	28,521(15%)
Single therapy – LABA	169(0%)	157(0%)
Single therapy – LAMA	2,722(1%)	2,775(1%)

*Data from April 2011 to March 2012
^Data from April 2012 to March 2013

Less than half of asthma therapy users with either multiple or single prescriptions used ICS+LABA combo, while less than one third of asthma therapy users with either multiple or single prescriptions used single therapy ICS.

Summary of Findings for Asthma Therapy Users by Year

1. From April 2011 to March 2012, the total number of asthma therapy users was 183,352. Users of ICS+LABA combo with multiple prescriptions accounted for 29% of asthma therapy users, while users of single therapy ICS and triple therapy ICS+LABA combo with multiple prescriptions both accounted for 15% of asthma therapy users. Both users of ICS+LABA combo and single therapy ICS with single prescriptions accounted for 15% of asthma therapy users, while users of multiple therapy - ICS+LABA combo + LAMA with single prescriptions accounted for 1% of asthma therapy users.
2. From April 2012 to March 2013, the total number of asthma therapy users was 191,073.Similarly to 2011/12, users of ICS+LABA combo with multiple prescriptions accounted for 30% of asthma therapy users, while users of single therapy ICS and triple therapy ICS+LABA combo with multiple prescriptions both accounted for 15% of asthma therapy users. Users of ICS+LABA combo and single therapy ICS with single prescriptions accounted for 16% and 15% of asthma therapy users, respectively. Whereas, users of multiple therapy - ICS+LABA combo + LAMA with single prescriptions accounted for 1% of asthma therapy users.

Table 10 Asthma Therapy Units by Year

	UNITS[1] N(%)	
	2011*	**2012^**
Total Asthma Therapy	95,609,100(100%)	98,373,080(100%)
ICS	27,284,880(29%)	26,439,620(27%)
LABA	1,234,680(1%)	1,118,220(1%)
LAMA	10,104,480(11%)	10,347,480(11%)
ICS+LABA	56,985,060(60%)	60,467,760(61%)

[1] Number of units = per puff
*Data from April 2011 to March 2012
^Data from April 2012 to March 2013

ICS+LABA accounted for the greatest number of units, followed by ICS, and then LAMA.

Summary of Findings for Asthma Therapy Units by Year

1. From April 2011 to March 2012, the total number of asthma therapy units was 95.6 million. ICS+LABA accounted for the greatest number of units, followed by ICS, and then LAMA. Overall, ICS+LABA accounted for 60% of the number of units of asthma therapy, while ICS accounted for 29%.
2. From April 2012 to March 2013, the total number of asthma therapy units was 98.4 million. Similarly to 2011/12, ICS+LABA accounted for the greatest number of units, followed by ICS, and then LAMA. Overall, ICS+LABA accounted for 61% of the number of units of asthma therapy, while ICS accounted for 27%.

Table 11 Asthma Therapy Prescriptions by Year

	PRESCRIPTIONS N(%)	
	2011*	**2012^**
Total Asthma Therapy	844,823(100%)	867,621(100%)
ICS	175,285(21%)	172,034(20%)
LABA	13,061(2%)	11,672(1%)
LAMA	199,563(24%)	204,074(24%)
ICS+LABA	456,914(54%)	479,841(55%)

*Data from April 2011 to March 2012
^Data from April 2012 to March 2013

The most commonly prescribed asthma therapy was ICS+LABA, followed by LAMA, and then ICS.

Summary of Findings for Number of Prescriptions by Year

1. From April 2011 to March 2012, a total of 844,823 prescriptions for asthma therapy were filled. ICS+LABA prescriptions accounted for more than half of all asthma therapy prescriptions, while ICS prescriptions accounted for 21% of all asthma therapy prescriptions.
2. From April 2012 to March 2013, a total of 867,621 prescriptions for asthma therapy were filled. Similarly to 2011/12, ICS+LABA prescriptions accounted for more than half of all asthma therapy prescriptions, while ICS prescriptions accounted for 20% of all asthma therapy prescriptions.

Table 12 Asthma Therapy Expenditure by Year

	Expenditure $(%)	
	2011*	**2012^**
Total Asthma Therapy	**$108,033,070(100%)**	**$112,557,431(100%)**
ICS	**$15,219,652(14%)**	**$14,976,511(13%)**
PULMICORT	$1,596,723(1%)	$1,515,366(1%)
FLOVENT DISKUS	$519,656(0%)	$530,486(0%)
QVAR	$624,713(1%)	$503,242(0%)
FLOVENT HFA	$11,295,282(10%)	$10,986,124(10%)
ALVESCO	$1,183,278(1%)	$1,441,293(1%)
LABA	**$1,126,075(1%)**	**$1,025,882(1%)**
SEREVENT	$4,650(0%)	$3,089(0%)
FORADIL	$27,850(0%)	$24,527(0%)
SEREVENT DISKUS	$702,453(1%)	$651,817(1%)
OXEZE	$391,122(0%)	$346,449(0%)
LAMA	**$22,921,618(21%)**	**$24,039,692(21%)**
SPIRIVA	$22,921,618(21%)	$24,039,692(21%)

	Expenditure $(%)	
	2011*	**2012^**
ICS+LABA	**$68,765,725(64%)**	**$72,515,346(64%)**
ADVAIR DISKUS	$50,618,173(47%)	$51,626,006(46%)
SYMBICORT	$18,134,531(17%)	$19,885,788(18%)
ZENHALE	$13,021(0%)	$1,003,552(1%)

*Data from April 2011 to March 2012
^Data from April 2012 to March 2013

From April 2011 to March 2012, total asthma therapy expenditure by OPDP was $108.0 million, and from April 2012 to March 2013, total asthma therapy expenditure by OPDP was $112.6 million.

Summary of Findings for Asthma Therapy Expenditure by Year

1. From April 2011 to March 2012, total asthma therapy expenditure by OPDP was $108.0 million, ranging from $1.1 million for LABA to $68.8 million for ICS+LABA. Overall, ICS+LABA accounted for 64% of all asthma therapy expenditure, while ICS accounted for 14% of all asthma therapy expenditure. Of all asthma therapy products, ADVAIR DISKUS accounted for the greatest expenditure ($50.6 million), followed by SPIRIVA with $22.9 million, and then SYMBICORT with $18.1 million.
2. From April 2012 to March 2013, total asthma therapy expenditure by OPDP was $112.6 million, ranging from $1.0 million for LABA to $72.5 million for ICS+LABA. Similarly to 2011/12, overall, ICS+LABA accounted for 64% of all asthma therapy expenditure, while ICS accounted for 13% of all asthma therapy expenditure. Of all asthma therapy products, ADVAIR DISKUS accounted for the greatest expenditure ($51.6 million), followed by SPIRIVA with $24.0 million, and then SYMBICORT with $19.9 million.

Table 13 Average Cost per Unit by Year

	Average Cost per Unit[1] $	
	2011*	**2012^**
Total Asthma Therapy	$1.13	$1.14
ICS	$0.56	$0.57
LABA	$0.91	$0.92
LAMA	$2.27	$2.32
ICS+LABA	$1.21	$1.20

[1]Average Cost per Unit = Average Cost per Puff
*Data from April 2011 to March 2012
^Data from April 2012 to March 2013

LAMA had the highest average cost per unit, followed by ICS+LABA; while ICS had the lowest average cost per unit.

Summary of Findings for Average Cost per Unit by Year

1. From April 2011 to March 2012, the average cost per unit was $1.13. LAMA had the highest average cost per unit at $2.27 and ICS had the lowest average cost per unit at $0.56, while the average cost per unit of ICS+LABA was $1.21.
2. From April 2012 to March 2013, the average cost per unit was $1.14. Similarly to 2011/12, LAMA had the highest average cost per unit at $2.32 and ICS had the lowest average cost per unit at $0.56, while the average cost per unit of ICS+LABA was $1.20.

Impact of Alternative Approaches to Reimbursement – Aggregated Results

Table 14 Budget Impact Analysis - Aggregated Results

REIMBURSEMENT SCENARIO	IMPACT	TOTAL^	% BUDGET IMPACT
STATUS QUO -			
CURRENT REIMBURSEMENT		**$112,557,431**	
BASE CASE			
STRATEGY #1 -			
COVERAGE OF ICS+LABA ONLY AFTER TRIAL OF MEDIUM DOSE ICS	Expected total $ Budget impact	**$112,142,990** - $414,441	**↓ 0.37%**
STRATEGY #2 -			
COVERAGE OF ICS+LABA ONLY AFTER TRIAL OF HIGH DOSE ICS	Expected total $ Budget impact	**$108,175,938** - $4,381,494	**↓ 3.89%**
SENSITIVITY ANALYSIS			
STRATEGY #1B -			
COVERAGE OF ICS+LABA ONLYAFTER TRIAL OF MEDIUM DOSE ICS	Expected total $ Budget impact	**$112,470,054** - $87,377	**↓ 0.08%**
STRATEGY #2B -			
COVERAGE OF ICS+LABA ONLY AFTER TRIAL OF HIGH DOSE ICS	Expected total $ Budget impact	**$114,627,302** + $2,069,870	**↑ 1.84%**

^Data from April 2012 to March 2013

Strategy #2, whereby all ICS+LABA low dose users switch to ICS medium dose and all ICS+LABA medium dose users switch to ICS high dose, would lead to the greater savings than Strategy #1 (an expenditure reduction of 3.89% or savings of $4.4 million). However, in sensitivity analysis, Strategy #2B would lead to an increase in costs over current expenditure whilst Strategy #1B would lead to negligible cost savings.

Summary of Findings for Budget Impact Analysis - Aggregated Results

1. From April 2012 to March 2013, total asthma therapy expenditure by OPDP was $112.6 million.
2. If patient uncontrolled on low dose ICS move to ICS medium dose rather than low dose ICS+LABA (**Strategy #1**), this would lead to a small decrease in total asthma therapy expenditure (a **reduction of 0.37%** or savings of $0.4 million).
3. If in addition, patients uncontrolled on medium dose ICS move to ICS high dose rather than medium dose ICS+LABA (**Strategy #2**), this would lead to the greatest savings expenditure (a **reduction of 3.89%** or savings of $4.4 million).
4. However, if half of those uncontrolled on low dose ICS move to medium dose ICS+LABA (**Strategy #1B**), this would lead to a smaller absolute reduction in total asthma therapy expenditure (a **reduction of 0.08%** or savings of $87.3 thousand).
5. Furthermore, if half of those uncontrolled on medium dose ICS move to high dose ICS+LABA (**Strategy #2B**), this would lead to an increase in asthma therapy expenditure (an **increase of 1.84%** or $2.1 million).

Base Case Results – Disaggregated Results

Table 15 Base Case - Disaggregated Results

	STATUS QUO	STRATEGY #1 - COVERAGE OF ICS+LABA ONLY AFTER TRIAL OF MEDIUM DOSE ICS	STRATEGY #2 - COVERAGE OF ICS+LABA ONLY AFTER TRIAL OF HIGH DOSE ICS
TOTAL ASTHMA THERAPY^	**$112,557,431**	**$112,142,990**	**$108,175,938**
ICS	**$14,976,511**	**$15,499,560**	**$38,350,839**
ICS (low dose)†	$117,627	$117,627	$117,627
ICS (medium dose)‡	$5,079,799	$5,602,848	$5,602,848
ICS (high dose) ‡	$9,779,085	$9,779,085	$32,630,364
LABA	**$1,025,882**	**$1,025,882**	**$1,025,882**
LAMA	**$24,039,692**	**$24,039,692**	**$24,039,692**
ICS+LABA	**$72,515,346**	**$71,577,856**	**$44,759,524**
ICS+LABA (low dose)†	$937,490	$0	$0
ICS+LABA (medium dose) ‡	$26,818,331	$26,818,331	$0
ICS+LABA (high dose) ‡	$44,759,524	$44,759,524	$44,759,524

^Data from April 2012 to March 2013

† As per Canadian Thoracic Society 2012 guideline

‡ As per Canadian Thoracic Society 2012 guideline, except SYMBICORT & ALVESCO products usage is split medium/high based on current usage data

Summary of Findings for Base Case - Disaggregated Results

1. From April 2012 to March 2013, total asthma therapy expenditure by OPDP was $112.6 million. Total ICS costs were $15.0 million and total ICS+LABA costs were $72.5 million.
2. Strategy #1, whereby patients uncontrolled on low dose ICS move to ICS medium dose rather than low dose ICS+LABA, would lead to an estimated cost of $112.1 million. Total ICS costs are estimated at $15.5 million and total ICS+LABA costs are estimated at $71.6 million.
3. Strategy #2, whereby in addition, patients uncontrolled on medium dose ICS move to ICS high dose rather than medium dose ICS+LABA, would lead to an estimated cost of $108.2 million. Total ICS costs are estimated at $38.4 million, while total ICS+LABA costs are estimated at $44.8 million.

Sensitivity Analysis Results – Disaggregated Results

Table 16 Sensitivity Analysis - Disaggregated Results

	STATUS QUO	STRATEGY #1B - COVERAGE OF ICS+LABA ONLYAFTER TRIAL OF MEDIUM DOSE ICS	STRATEGY #2B - COVERAGE OF ICS+LABA ONLY AFTER TRIAL OF HIGH DOSE ICS
TOTAL ASTHMA THERAPY^	**$112,557,431**	**$112,470,054**	**$114,627,302**
ICS	**$14,976,511**	**$15,238,035**	**$26,925,199**
ICS (low dose)†	$117,627	$117,627	$117,627
ICS (medium dose)‡	$5,079,799	$5,341,324	$5,602,848
ICS (high dose) ‡	$9,779,085	$9,779,085	$21,204,724
LABA	**$1,025,882**	**$1,025,882**	**$1,025,882**
LAMA	**$24,039,692**	**$24,039,692**	**$24,039,692**
ICS+LABA	**$72,515,346**	**$72,166,444**	**$62,636,528**
ICS+LABA (low dose)†	$937,490	$0	$0
ICS+LABA (medium dose) ‡	$26,818,331	$27,222,157	$0
ICS+LABA (high dose) ‡	$44,759,524	$44,944,286	$62,636,528

^Data from April 2012 to March 2013

† As per Canadian Thoracic Society 2012 guideline

‡ As per Canadian Thoracic Society 2012 guideline, except SYMBICORT & ALVESCO products usage is split medium/high based on current usage data

Summary of Findings for Sensitivity Analysis - Disaggregated Results

1. From April 2012 to March 2013, total asthma therapy expenditure by OPDP was $112.6 million. Total ICS costs were $15.0 million and total ICS+LABA costs were $72.5 million.
2. Strategy #1B, whereby half of patients uncontrolled on low dose ICS move to ICS medium dose +LABA, would lead to an estimated cost of $112.5 million. Total ICS costs are estimated at $15.2 million and total ICS+LABA costs are estimated at $72.2 million.
3. Strategy #2b, whereby half of patients uncontrolled on medium dose ICS move to ICS high dose +LABA, would lead to an estimated cost of $114.6 million. Total ICS costs are estimated at $26.9 million, while total ICS+LABA costs are estimated at $62.6 million.

Overall Conclusions and Summary

Total OPDP expenditure on asthma therapy (ICS, LABA, ICS+LABA and LAMA) was $112.6 million (from April 2012 to March 2013). The average cost per unit of ICS+LABA was $1.20, whereas the average cost per unit of ICS was $0.57.

Assuming a policy whereby combination products involving low dose ICS+LABA are not funded and assuming all patients uncontrolled on low dose ICS move to medium dose ICS would lead to a small absolute reduction in total asthma therapy expenditure (savings of $0.4 million). Smaller cost savings are expected however if half of the patients uncontrolled on low dose ICS move to medium dose ICS+ (savings of $87.3 thousand).

Assuming a policy whereby combination products involving low and medium dose ICS+LABA are not funded and assuming all patients uncontrolled on low dose ICS move to medium dose ICS and uncontrolled on medium dose move to high dose ICS would lead to greater savings (a reduction of $4.4 million). However, if half of the patients uncontrolled on medium dose ICS move to high dose ICS+LABA costs will increase (an increase of $2.1 million).

Conclusions

Assuming a policy of not funding low and medium dose ICS+LABA combination products would lead to the greatest savings (a reduction of $4.4 million per annum), assuming patients uncontrolled on low and moderate dose ICS move to a higher dose ICS. However, under a scenario whereby 50% of patients uncontrolled on moderate ICS move to a high dose ICS+LABA combination product, costs are forecasted to rise. Similarly if patients were prescribed separate inhalers when certain combination products are not funded, costs will likely rise.

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