

Drug Class Review

Controller Medications for Asthma

Final Report
Executive Summary

November 2008



The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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INTRODUCTION

Asthma is a chronic lung disease characterized by reversible airway obstruction, inflammation, and increased airway responsiveness. Many current medications available to treat persistent asthma target the inflammatory process caused by multiple inflammatory cells and mediators including lymphocytes, mast cells, and eosinophils, among others. There are currently two categories of medications used in asthma treatment: controller medications and quick relief (or rescue) medications. Although all patients with persistent asthma should have a short-acting relief medication on hand for treatment of exacerbations and a controller medication for long-term control, this report will focus on the following currently available controller medications: inhaled corticosteroids (ICSs), long-acting beta-2 agonists (LABAs), leukotriene modifiers, anti-IgE medications, and combination products.

ICSs are the preferred agents for long-term control of persistent asthma according to the National Asthma Education and Prevention Program (NAEPP) expert panel recommendations. The inhaled route of administration serves to directly target the inflammation while minimizing systemic effects which can result from oral administration. These agents act via anti-inflammatory mechanisms and have been approved as first line therapy for asthma control in all stages of persistent asthma. The six ICSs currently available include: beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide.

LABAs are agents used in combination with ICSs to obtain control in persistent asthma. The mechanism of action of these agents is through relaxation of airway smooth muscles to reverse bronchoconstriction. In contrast to short-acting beta-2 agonists, which are used for quick relief of acute symptoms due to their quick onset and short-duration of action, LABAs provide long-acting bronchodilation for 12 hours allowing for twice daily administration. The NAEPP expert panel advocates the use of LABAs as the preferred adjunct therapy with ICSs in individuals ≥ 12 years old for persistent asthma. These agents are not recommended nor approved for relief of acute asthma symptoms or for use as monotherapy for persistent asthma. Currently there are two available LABAs: formoterol (formerly known as eformoterol in the UK) and salmeterol. Arformoterol is available in the US but is currently approved only for chronic obstructive pulmonary disease (COPD).

The leukotriene modifiers are another class of controller medications used in the treatment of asthma and are comprised of two classes of medications: leukotriene receptor antagonists (montelukast and zafirlukast) and 5-lipoxygenase inhibitors (zileuton). Leukotrienes cause contraction of smooth muscles, mucous secretion, and inflammation contributing to asthma symptoms. The leukotriene receptor antagonists (LTRAs) bind to cell receptors to prevent these actions from occurring. Montelukast is approved for children ≥ 1 year old and zafirlukast for children ≥ 5 years old in the US and ≥ 12 years old in Canada. They are approved for mild persistent asthma and as adjunct therapy with ICSs. The leukotriene modifiers are the only medications delivered orally in pill-form, rather than as inhalers, for the treatment of persistent asthma.

The newest class of asthma control medications is the anti-IgE medication class which currently consists of one agent, omalizumab. This agent binds to IgE receptors on mast cells and basophils to decrease sputum production and asthma symptoms. Omalizumab is approved for use in patients ≥ 12 years old who have uncontrolled asthma on ICSs. It is an injectable medication (given every two to four weeks) approved for adjunct therapy with ICSs in moderate to severe

persistent asthma as well as for adjunct therapy with high dose ICSs plus LABA in severe persistent asthma.

Lastly, the combination controller medications available for the treatment of asthma include fluticasone/salmeterol (FP/SM) and budesonide/formoterol (BUD/FM). These medications are both combinations of an ICS and a LABA and are indicated for use in those patients requiring two agents for control.

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of controller medications for persistent asthma.

The participating organizations approved the following key questions to guide this review:

1. What is the comparative efficacy and effectiveness of controller medications used to treat outpatients with persistent asthma?
2. What is the comparative tolerability and frequency of adverse events for controller medications used to treat outpatients with persistent asthma?
3. Are there subgroups of these patients based on demographics (age, racial groups, gender), asthma severity, comorbidities (drug-disease interactions, including obesity), smoking status, genetics, or pregnancy for which asthma controller medications differ in efficacy, effectiveness, or frequency of adverse events?

METHODS

To identify relevant citations, we searched MEDLINE[®], the Cochrane Database of Systematic Reviews[®], the Cochrane Central Register of Controlled Trials[®], and the International Pharmaceutical Abstracts (through April 2008). We attempted to identify additional studies through manual searches of reference lists of included studies and reviews. In addition, we searched the FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), the Canadian Agency for Drugs and Technology in Health, and the National Institute for Health and Clinical Excellence web sites for medical and statistical reviews, and technology assessments. Finally, we searched dossiers submitted by pharmaceutical companies for the current review. All citations were imported into an electronic database (Endnote[®] v. X.02).

For efficacy and effectiveness, RCTs of at least 6 weeks' duration and a study population with a sample size greater than 40 participants were eligible for inclusion. For adverse events, observational studies of at least 6 months duration with a study population of at least 100 participants were also eligible. Two reviewers independently assessed abstracts and full-text articles. Trained reviewers abstracted data from each study and assigned an initial quality rating. A second reviewer read each abstracted article, evaluated the completeness of the data abstraction, and confirmed the quality rating. We assessed the internal validity (quality) of trials based on predefined criteria. These criteria are based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK) criteria.

We summarize the overall strength of evidence for the efficacy/effectiveness of each head-to-head comparison. The overall strength of evidence for a particular key question reflects the design, quality, consistency, directness, and magnitude of effect of the set of studies relevant to the question. We rate the overall strength of evidence as low, moderate, high, or insufficient using a modified GRADE approach established by the Evidence-based Practice Centers. *High* strength of evidence indicates high confidence in the estimate of effect and that the evidence reflects the true effect; further research is unlikely to change our confidence. *Moderate* strength of evidence indicates moderate confidence that the evidence reflects the true effect; further research may change our confidence in the estimate and may change the estimate. *Low* strength of evidence indicates low confidence that the evidence reflects the true effect; further research is likely to change our confidence in the estimate and is likely to change the estimate. *Insufficient* indicates that evidence is unavailable or does not permit estimation of an effect.

RESULTS

In total we included 201 studies (222 articles): 20 systematic reviews with meta-analyses, 146 randomized controlled trials (166 articles), nine observational studies (10 articles), and one study of other design. Twenty-five studies that met the eligibility criteria were subsequently rated as poor quality for internal validity.

Key Question 1.

What is the comparative efficacy and effectiveness of controller medications used to treat outpatients with persistent asthma?

I. Intra-class comparisons (within one class)

Inhaled Corticosteroids (ICSs)

We found 2 systematic reviews with meta-analyses and 30 head-to-head RCTs (29 publications). Four of the head-to-head RCTs included children < 12 years of age. No study was characterized as an effectiveness trial; all included efficacy studies were conducted in narrowly defined populations and/or were limited to less than one year of follow-up. Overall, efficacy studies provide a moderate strength of evidence that ICSs do not differ in their ability to control asthma symptoms, prevent exacerbations, and reduce the need for additional rescue medication at equipotent doses administered through comparable delivery devices. Relatively few studies reported exacerbations, healthcare utilization (hospitalizations, emergency visits), or quality of life outcomes. Long-term data beyond 12 weeks is lacking for most of the comparisons. In children, the body of evidence supports the above conclusion, but data was only available for three comparisons (two systematic reviews and four RCTs): beclomethasone compared with budesonide, beclomethasone compared with fluticasone, and budesonide compared with fluticasone.

Leukotriene modifiers

Limited head-to-head evidence from one short-term study (12 weeks) in adults and adolescents \geq 12 years of age does not support a difference between montelukast and zafirlukast in their ability

to decrease rescue medicine use or improve quality of life (low strength of evidence for those \geq 12 years). We found no head to head trials in children $<$ 12 years of age (insufficient evidence).

Long-acting beta-2 agonists (LABAs)

Results from 3 efficacy studies provide moderate evidence that LABAs do not differ in their ability to control asthma symptoms, prevent exacerbations, improve quality of life, and prevent hospitalizations or emergency visits in patients with persistent asthma not controlled on ICSs alone. Large systematic reviews comparing LABAs with other treatments provide some indirect evidence supporting this conclusion. For children, direct evidence is limited to one fair trial enrolling children and adolescents 6-17 years of age. The trial reported no difference in symptoms, exacerbations, quality of life, missed work, or missed school, but found a greater decrease in rescue medicine use in subjects treated with eformoterol compared to those treated with salmeterol.

Anti-IgE therapy (omalizumab)

Meta-analyses and efficacy studies provide consistent evidence favoring omalizumab over placebo for the ability to control asthma symptoms, prevent exacerbations, and reduce the need for additional rescue medication in adults and adolescents \geq 12 years of age (high strength of evidence). Limited evidence from one fair trial is available for children $<$ 12 years of age. The trial reported no difference in measures of symptoms, but fewer exacerbations, less rescue medicine use, greater quality of life, and fewer emergency visits and hospitalizations for subjects treated with omalizumab (low strength of evidence for patients $<$ 12 years).

Combination products

Budesonide/formoterol (BUD/FM) compared with fluticasone/salmeterol (FP/SM)

Results from 4 large randomized controlled trials up to 6 months in duration comparing equipotent steroid components support no significant difference in efficacy between BUD/FM and FP/SM. The results of our meta-analysis show no difference in exacerbations between those treated with BUD/FM and those treated with FP/SM (SMD = -0.0286, 95% CI: -0.0872, 0.0299, 4 studies). None of the trials included children $<$ 12 years of age (high strength of evidence for \geq 12 years; insufficient strength of evidence for children $<$ 12 years).

Combination Products

BUD/FM for maintenance and relief compared with ICS/LABA combination (BUD/FM or FP/SM) for maintenance with short-acting beta-agonist (SABA) for relief

We found 4 fair or good quality RCTs (making 5 relevant comparisons). Of note, BUD/FM is not approved for use as a relief medication in the US, but has been approved for maintenance and reliever therapy in Canada. Meta-analysis of results from large trials (10,547 subjects) up to 12 months in duration including children and adults found statistically significantly lower exacerbation rates (SMD = -0.1216, 95% CI: -0.1595, -0.0837; 5 comparisons) for those treated with BUD/FM for maintenance and relief than for those treated with ICS/LABA (BUD/FM or FP/SM) for maintenance with SABA for relief. There were no differences in symptom-free days, symptom scores, nocturnal awakenings, rescue-free days, or rescue medicine use. The one trial that included children (down to 4 years of age) found similar results. It is difficult to determine the applicability of the results of these trials given the heterogeneity of study designs and dose comparisons. In addition, several of the trials significantly reduced the total ICS doses for many

subjects upon randomization; some studies reduced the starting doses to levels that could be considered inadequate compared to the subjects' previous dose requirements for control. In general, we can not conclude that there is a significant difference in overall efficacy between these two treatment strategies (moderate strength of evidence for all ages).

II. Inter-class comparisons (between classes)

ICSs compared with leukotriene modifiers for monotherapy

We found 2 systematic reviews with meta-analyses and 21 RCTs. Thirteen of the RCTs were in adolescents and adults ≥ 12 years of age and 8 were in children < 12 years. Efficacy studies up to 56 weeks in duration provide consistent evidence favoring ICSs over leukotriene modifiers for the treatment of asthma as monotherapy for both children and adults (high strength of evidence for all ages). Those treated with leukotriene modifiers had a significantly higher occurrence of exacerbations than those treated with ICSs (SMD = 0.216, 95% CI: 0.127, 0.305, 12 studies). In addition, our meta-analyses found statistically significant differences in favor of ICSs for measures of symptoms, rescue medicine use, and quality of life.

ICSs compared with LABAs for monotherapy

Efficacy studies (11 RCTs) up to 12 months in duration provide consistent evidence favoring ICSs over LABAs for the treatment of asthma as monotherapy for children and adults (high strength of evidence for all ages). Those treated with LABAs had a significantly higher occurrence of exacerbations than those treated with ICSs (SMD = 0.221, 95% CI: 0.025, 0.417; $P = 0.027$, 6 studies). Of note, LABAs are not recommended nor approved for use as monotherapy for persistent asthma because they may increase the risk of asthma-related deaths.

Leukotriene modifiers compared with LABAs for monotherapy

Two small trials provide insufficient evidence to draw firm conclusions about the comparative efficacy of leukotriene modifiers and LABAs (insufficient strength of evidence for all ages). Of note, LABAs are not recommended nor approved for use as monotherapy for persistent asthma because they may increase the risk of asthma-related deaths.

ICS + LABA compared with ICS (same dose) as first line therapy

Meta-analyses of results from large trials up to 12 months in duration found mixed results and do not provide sufficient evidence to support the general use of combination therapy rather than ICS alone as first line therapy (moderate strength of evidence for ≥ 12 years; insufficient strength of evidence for < 12 years). Meta-analyses found statistically significantly greater improvements in symptoms and rescue medicine use, but no difference in exacerbations for adolescents and adults treated with ICS+LABA than for those treated with ICS alone for initial therapy. However, limited data was available for exacerbations and further research may change our confidence in the estimate of effect for this outcome. Of note, ICS+LABA combination products are only indicated for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose ICSs) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. We found no studies for this comparison that enrolled children < 12 years of age.

ICS + LABA compared with ICS (increased dose)
(addition of LABA to ICS compared with increasing the ICS dose)

Results from large trials (27 RCTs) up to 12 months in duration support greater efficacy with the addition of a LABA to an ICS than with increasing the ICS dose for adults and adolescents with persistent asthma (high strength of evidence for ≥ 12 years; low strength of evidence for < 12). Our meta-analysis shows statistically significantly greater improvement in symptom-free days, symptom scores, rescue-free days, and rescue medicine use for subjects treated with ICS+LABA. Despite a trend toward fewer subjects with exacerbations in the ICS+LABA group, the difference was not statistically significant in our analysis. Just one trial exclusively enrolled children < 12 (four included some subjects < 12) and all results are not necessarily generalizable to pediatric populations.

ICS + LABA compared with ICS (same dose)
(addition of LABA to ICS compared with continuing same dose ICS)

Results from large trials (26 RCTs) up to one year in duration support greater efficacy with the addition of a LABA to an ICS over continuing the current dose of ICS alone for patients with poorly controlled persistent asthma (high strength of evidence for all ages). Five trials included pediatric populations < 12 years of age.

ICS + leukotriene modifiers compared with ICS (same dose)

The addition of leukotriene modifiers to ICSs compared to continuing the same dose of ICSs resulted in improvement in rescue medicine use and a non-statistically significant trend toward fewer exacerbations requiring systemic steroids. There were no statistically significant differences in other health outcomes. None of the included trials enrolled children < 12 years of age. The overall strength of evidence for these differences is low for patients ≥ 12 years of age and insufficient for those < 12 .

ICS + leukotriene modifiers compared with ICS (increased dose)

There is no apparent difference in health outcomes between those treated with ICSs plus leukotriene modifiers compared to those treated with increasing the dose of ICSs (moderate strength of evidence for ≥ 12 years; low strength of evidence for < 12). There were some conflicting results and further research may alter the findings. The only included trial enrolling children < 12 years of age was a 12-week trial conducted in India that reported fewer exacerbations in those treated with ICS+ leukotriene modifiers compared to increasing the dose of BUD.

Combination products (ICS/LABA) compared with leukotriene modifiers

We found 4 RCTs meeting our inclusion/exclusion criteria for this comparison. All compared low dose fluticasone plus salmeterol with montelukast. Two of the RCTs were in adolescents and adults, one enrolled subjects over the age of six (~15% of subjects < 12 years of age), and one enrolled children ages 6-14. Overall, our meta-analysis and results from 4 RCTs find the combination of fluticasone plus salmeterol to be more efficacious than montelukast for the treatment of persistent asthma (high strength of evidence for ≥ 12 years; moderate strength of evidence for < 12). One of the trials enrolled children ages 6-14 and another included about 15% of subjects < 12 years of age.

*ICS + LABA compared with ICS + leukotriene modifier
(addition of LABA compared with leukotriene modifier to ongoing ICS therapy)*

Overall, results from a good quality systematic review with meta-analysis and 7 RCTs provide strong evidence that the addition of a LABA to ICS therapy is more efficacious than the addition of a leukotriene modifier to ICS therapy for adolescents and adults with persistent asthma (high strength of evidence for ≥ 12 years; insufficient strength of evidence for < 12). We found no trials in children < 12 years of age and none contributed data to the meta-analysis.

Leukotriene modifier + LABA compared with ICS + LABA

Results from one 32 week cross-over trial, which was terminated early, reported that subjects treated with leukotriene modifier + LABA had significantly shorter time to treatment failure than those treated with ICS + LABA ($P = 0.0008$). Indirect evidence from other comparisons supports our conclusion that the ICS+LABA combination is more efficacious than the leukotriene modifier + LABA combination (moderate strength of evidence for ≥ 12 years; insufficient strength of evidence for < 12). We found no studies for this comparison that enrolled children < 12 years of age.

Key Question 2.

What is the comparative tolerability and frequency of adverse events for controller medications used to treat outpatients with persistent asthma?

1. Intra-class comparisons (within one class)

Inhaled corticosteroids (ICSs)

The overall incidence of adverse events, withdrawals due to adverse events, and specific adverse events (other than reduction in growth velocity) are similar for equipotent doses of ICSs (moderate strength of evidence). Three fair head-to-head trials provide evidence that short-term growth velocity is reduced slightly less with fluticasone than with beclomethasone or budesonide. In addition, 2 meta-analyses report a reduction in growth velocity for beclomethasone or fluticasone compared to placebo. The best longer-term evidence (average 4.3 years) is from the CAMP study, which found a 1.1 cm difference in mean increase in height between BUD- and placebo-treated patients ($P = 0.005$). The differences in growth occurred primarily during the first year of treatment, suggesting that the small decrease in growth velocity with ICSs occurs early in treatment and is not progressive (moderate strength of evidence). Evidence is insufficient to determine if long-term treatment with ICSs leads to a reduction in final adult height.

Leukotriene modifiers

There is insufficient head-to-head data (one trial) to determine differences in tolerability or overall adverse events between any of the leukotriene modifiers using direct evidence. Indirect evidence from placebo-controlled trials and large safety databases suggests that zileuton has an increased risk of liver toxicity compared with either montelukast or zafirlukast (moderate strength of evidence).

Long-acting beta-2 agonists (LABAs)

Limited direct evidence from head-to-head trials and indirect evidence from systematic reviews provides no evidence of a difference in tolerability or adverse events between formoterol and salmeterol (moderate strength of evidence).

Anti-IgE therapy (omalizumab)

Omalizumab is the only available anti-IgE drug approved for the treatment of asthma; therefore, there are no studies of intra-class comparisons. Omalizumab-treated patients have an increased incidence of injection site reactions and anaphylaxis compared to placebo-treated patients (high strength of evidence). Omalizumab has a boxed (or “black box”) warning for anaphylaxis. Omalizumab also has a warning for a potential increased risk of malignancy, based on short term data from studies less than one year in duration (low strength of evidence).

Combination products

Budesonide/formoterol (BUD/FM) compared with fluticasone/salmeterol (FP/SM)

Data from 4 large head-to-head trials (5,818 subjects) provide no evidence of a difference in tolerability or overall adverse events between BUD/FM and FP/SM in adults and adolescents (high strength of evidence for adults and adolescents ≥ 12 years; insufficient for < 12 years). There is insufficient evidence to draw conclusions in children < 12 .

II. Inter-class comparisons (between classes)

ICSs compared with leukotriene modifiers for monotherapy

Data from one good quality systematic review and numerous head-to-head RCTs provide no evidence of a difference in tolerability or overall adverse events (risk of experiencing any adverse effects: RR 0.99, 95% CI: 0.93, 1.04, 15 trials) between ICSs and leukotriene modifiers (moderate strength of evidence). Trials were generally not designed to compare tolerability and adverse events. Specific adverse events reported with ICSs, such as cataracts and decreased growth velocity, were not found among patients taking leukotriene modifiers. One 56-week RCT found that the mean growth rate of subjects treated with beclomethasone was 0.81 cm less than that of subjects treated with montelukast.

ICSs compared with LABAs for monotherapy

Overall evidence indicates that ICSs are safer than LABAs for use as monotherapy (high strength of evidence). Of note, LABAs are not recommended nor approved for use as monotherapy for persistent asthma because they may increase the risk of asthma-related deaths.

Leukotriene modifiers compared with LABAs for monotherapy

Indirect evidence indicates that leukotriene modifiers are safer than LABAs for use as monotherapy (high strength of evidence). Of note, LABAs are not recommended nor approved for use as monotherapy for persistent asthma because they may increase the risk of asthma-related deaths.

ICS + LABA compared with ICS (same dose) as first line therapy

Results from a good quality systematic review with meta-analysis and 5 RCTs found no difference in overall adverse events or withdrawals due to adverse events between subjects

treated with ICSs plus LABAs and subjects treated with ICSs alone as first line therapy (moderate strength of evidence for ≥ 12 years; insufficient strength of evidence for < 12). Trials were 12-24 weeks in duration and were generally not designed to compare tolerability and adverse events. Indirect evidence from a recent systematic review that included a post-hoc analysis of data from the Salmeterol Multicenter Asthma Research Trial (SMART) suggests that the potential increased risk of asthma-related death for those taking LABAs may be confined to patients not taking ICSs at baseline. Of note, ICS+LABA combination products are only indicated for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose ICSs) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. We found no studies for this comparison that enrolled children < 12 years of age.

ICS + LABA compared with ICS (increased dose)
(addition of LABA to ICS compared with increasing the ICS dose)

Results from a good quality systematic review with meta-analysis and numerous RCTs found no difference in overall adverse events or withdrawals between subjects treated with ICSs plus LABAs and subjects treated with an increased dose of ICSs (moderate strength of evidence for ≥ 12 years; low strength of evidence for < 12). Those treated with ICSs + LABAs had an increased rate of tremor (N = 10, RR 2.96, 95% CI: 1.60, 5.45). Indirect evidence from a recent systematic review that included a post-hoc analysis of data from SMART suggests that the potential increased risk of asthma-related death for those taking LABAs may be confined to patients not taking ICSs at baseline. Just one of the RCTs enrolled an exclusively pediatric population < 12 years of age (four included some subjects < 12) and results are not necessarily applicable to pediatric populations.

ICS + LABA compared with ICS (same dose)
(addition of LABA to ICS compared with continuing same dose ICS)

Results from a good quality systematic review with meta-analysis and numerous RCTs (including five that enrolled some subjects under 12 years of age) found no difference in overall adverse events or withdrawals between subjects treated with ICSs plus LABAs and subjects treated with the same dose of ICSs (moderate strength of evidence for ≥ 12 years; low strength of evidence for < 12). Although not statistically significantly different, the upper limits of the confidence intervals for tachycardia or palpitations (N = 5, RR 2.13, 95% CI: 0.77, 5.88) and tremor (N = 7, RR 2.48, 95% CI: 0.78, 7.89) were relatively high, suggesting that these may be more frequent in patients treated with ICSs plus LABAs. Indirect evidence from a recent systematic review that included a post-hoc analysis of data from SMART suggests that the potential increased risk of asthma-related death for those taking LABAs may be confined to patients not taking ICSs at baseline.

ICS + leukotriene modifiers compared with ICS (same dose)

Evidence from one good quality systematic review with meta-analysis (including 27 trials) found that the addition of leukotriene modifiers to ICSs compared to continuing the same dose of ICSs resulted in no significant differences in overall adverse events or withdrawals due to adverse events (moderate strength of evidence for ≥ 12 years; low strength of evidence for < 12). Trials were generally not designed to compare tolerability and adverse events and many used higher

than licensed doses of leukotriene modifiers. Evidence in children < 12 years of age is limited. Just 2 of the 27 trials in the systematic review enrolled children.

ICS + leukotriene modifiers compared with ICS (increased dose)

Evidence from one good quality systematic review with meta-analysis (including 27 trials) found that the addition of leukotriene modifiers to ICSs compared to increasing the dose of ICSs resulted in no significant differences in overall adverse events or withdrawals due to adverse events (moderate strength of evidence for ≥ 12 years; low strength of evidence for < 12). Trials were generally not designed to compare tolerability and adverse events and many used higher than licensed doses of leukotriene modifiers. Evidence in children < 12 years of age is limited. Just 2 of the 27 trials in the systematic review enrolled children.

Combination products (ICS/LABA) compared with leukotriene modifiers

ICS/LABA combinations and leukotriene modifiers have similar rates of overall adverse events and withdrawals due to adverse events based on limited direct evidence from 3 short-term trials (low strength of evidence). One of the three trials enrolled subjects at least 6 years of age (about 15% were <12 years old).

ICS + LABA compared with ICS + leukotriene modifiers

(addition of LABA compared with addition of a leukotriene modifier to ongoing ICS therapy)

Results from a good quality systematic review with meta-analysis and 6 RCTs provide moderate evidence that there is no difference in overall adverse events or withdrawals due to adverse events between ICS+LABA and ICS + leukotriene modifiers (moderate strength of evidence for ≥ 12 years; insufficient strength of evidence for < 12). Trials were generally not designed to compare tolerability and adverse events. We found no RCTs enrolling children <12 years of age; the systematic review included just one trial in children (that did not contribute data to the meta-analysis). Thus, there is insufficient evidence to draw conclusions in children < 12 years of age.

Key Question 3.

Are there subgroups of these patients based on demographics (age, racial groups, gender), asthma severity, comorbidities (drug-disease interactions, including obesity), other medications (drug-drug interactions), smoking status, genetics, or pregnancy for which asthma controller medications differ in efficacy, effectiveness, or frequency of adverse events?

Age

Differences in the efficacy, tolerability, or adverse events between children <12 years of age and adolescents or adults ≥ 12 are described above under Key Questions 1 and 2. For children ≤ 4 years of age, we found no head-to-head studies comparing the efficacy or safety of our included drugs in this age group with older children, adolescents, or adults (insufficient strength of evidence).

Racial groups

A large randomized trial (26,355 subjects) comparing salmeterol with placebo (SMART) was discontinued early due to findings in African-Americans, safety concerns, and difficulties in

enrollment. The trial reported an increased risk of asthma-related deaths (13 compared with 3; RR 4.37; 95% CI: 1.25 to 15.34). The increased risk was thought to be largely attributable to the African-American subpopulation. Although the study was not designed to assess subgroups, there were approximately four-fold relative increases in respiratory-related deaths or life-threatening experiences (20 compared with 5; RR 4.10; 95% CI: 1.54 to 10.90) and combined asthma-related deaths or life-threatening experiences (19 compared with 4; RR 4.92; 95% CI: 1.68 to 14.45) in African-Americans treated with salmeterol compared to those treated with placebo (low strength of evidence).

Gender

We did not find any study reporting a difference between the included medications (insufficient strength of evidence).

Comorbidities

We did not find any studies meeting our inclusion/exclusion criteria that directly compared the efficacy, effectiveness, or tolerability of our included drugs in populations with specific comorbidities (insufficient strength of evidence).

Other medications (drug-drug interactions)

We did not find any studies meeting our inclusion/exclusion criteria that examined the impact of other medications on the comparative efficacy, tolerability, or adverse events of our included medications (insufficient strength of evidence).

Smoking status

One study comparing ML and BDP in smokers and non-smokers provides some information that there may be differential responses to treatment between smokers and non-smokers (low strength of evidence).

Pregnancy

We did not find any studies that directly examined the comparative efficacy, tolerability, or adverse events of our included medications (insufficient strength of evidence). Budesonide is the only ICS labeled pregnancy category B; the other ICSs are category C.

Genetics

To date, there is not sufficient evidence to determine whether genetic polymorphisms result in clinically important differences in responses to asthma medications (insufficient strength of evidence). Multiple studies have investigated the impact of polymorphisms (e.g. the Beta-2 adrenoreceptor gene, ADRB2) on response to various asthma treatments, but none have demonstrated clinical validity or clinical utility of testing for polymorphisms.