CEDAC FINAL RECOMMENDATION

MOMETASONE FUROATE/FORMOTEROL FUMARATE DIHYDRATE INHALATION AEROSOL

(Zenhale – Merck Canada Inc.)

Indication: Asthma Maintenance (Adults, Children 12 Years or Older)

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that mometasone furoate/formoterol fumarate dihydrate (Zenhale) not be listed.

Reasons for the Recommendation:

1. The Committee considered the comparative clinical benefit of mometasone/formoterol to be uncertain. The only randomized controlled trial (RCT) designed to compare the efficacy of mometasone/formoterol with fluticasone/salmeterol in asthma (study 4705) was limited by its early termination at 12 weeks, open-label design, and a non-inferiority margin for the primary outcome that was of uncertain clinical relevance.

2. There are no RCTs in patients with asthma that compare the efficacy and safety of mometasone/formoterol with an inhaled corticosteroid monotherapy marketed in Canada.

Background:
Zenhale is a fixed-dose combination of an inhaled corticosteroid (mometasone furoate) and a long-acting beta-agonist (LABA) (formoterol fumarate dihydrate) that has a Health Canada indication for the maintenance treatment of asthma in adults and children 12 years of age and older with reversible obstructive airway disease whose asthma cannot be adequately controlled on asthma controller medications. It is available as a 120-dose inhaler providing pressurized metered dose suspension for inhalation in the following dose combinations of mometasone and formoterol, respectively, per actuation: 50/5 mcg, 100/5 mcg, and 200/5 mcg.

The Health Canada-recommended dose is two inhalations twice daily (morning and evening) by oral inhalation. The maximum daily recommended dose is 800/20 mcg (given as two inhalations of mometasone/formoterol 200/5 mcg twice daily) for patients 12 years of age and older.

© 2011 CADTH

Summary of CEDAC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of mometasone/formoterol, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials
The systematic review included four RCTs of patients 12 years and older with asthma and a minimum 12-week history of inhaled corticosteroid use (low dose in study 4073, medium dose in studies 4705 and 4334, and medium or high dose in study 4139) with or without a LABA.

- Study 4705 (N = 722) was open label and randomized patients to mometasone/formoterol 200/10 mcg twice daily or fluticasone/salmeterol 250/50 mcg twice daily. Despite a planned 52-week duration, the manufacturer halted the study after 12 weeks.
- Study 4139 (N = 404) was open label and used stratified randomization based on patients' recent inhaled corticosteroid use. Patients using medium doses of inhaled corticosteroids were randomized to either mometasone/formoterol 200/10 mcg or fluticasone/salmeterol 250/50 mcg twice daily. Patients on high doses of inhaled corticosteroid were randomized to either mometasone/formoterol 400/10 mcg or fluticasone/salmeterol 500/50 mcg twice daily. Study duration was 52 weeks.
- Study 4334 (N = 781) was double blind and randomized patients to one of four treatment groups: mometasone/formoterol 200/10 mcg, mometasone 200 mcg, formoterol 10 mcg, or placebo (all twice daily) for 26 weeks.
- Study 4073 (N = 746) was double blind and randomized patients to one of four treatment groups: mometasone/formoterol 100/10 mcg, mometasone 100 mcg, formoterol 10 mcg, or placebo (all twice daily) for 26 weeks.

All studies, except study 4139, included a two- to three-week open-label run-in period, during which patients received mometasone monotherapy prior to randomization. All trials allowed the use of short-acting beta-agonists on an "as-needed" basis. However, systemic steroid use resulted in early termination of patients from trials.

Study 4705 was limited by its early termination at 12 weeks. The frequency of study withdrawal in study 4139 was approximately 15% and similar between treatment groups. Study withdrawal was approximately 29% in the placebo-controlled trials; withdrawal was higher in the placebo groups compared with mometasone/formoterol in both 4334 and 4073 (39% versus 18%, and 38% versus 20%, respectively).

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: frequency of exacerbations, asthma symptoms, quality of life, rescue medication use, and change in lung function tests.

© 2011 CADTH

The primary outcome of study 4705 was the change from baseline in forced expiratory volume in one second (FEV_1) area under the curve (AUC; 0 to 12 hours) for which the threshold for non-inferiority was –1.5 litres x hours for the lower bound of the 95% confidence interval (CI) of the between-treatment difference. Study 4139 was a safety study and the primary outcome was the incidence of adverse events. The co-primary outcomes for studies 4334 and 4073 were time to first asthma deterioration, and change from baseline in FEV_1 AUC.

The Asthma Quality of Life Questionnaire with Standardized activities [AQLQ(S)] scores items in four domains (activity limitation, symptoms, emotional function, and environmental stimuli) from 1 to 7, with lower scores indicating greater impairment. The reported minimal clinically important difference for the AQLQ(S) varies from 0.5 to 1.0.

Results

The Committee focused its discussion on comparisons between mometasone/formoterol and either fluticasone/salmeterol or placebo because mometasone monotherapy for inhalation is not marketed in Canada and LABA monotherapy is not considered an option for asthma therapy because of safety concerns.

Efficacy or Effectiveness

- Improvement in lung function, as measured by the change from baseline in the FEV_1 AUC, was not statistically significantly different between mometasone/formoterol and fluticasone/salmeterol in either study 4705 or 4139. Based on the between-treatment difference in the change from baseline in the FEV_1 AUC (0 to 12 hours), mometasone/formoterol was reported to be non-inferior to fluticasone/salmeterol in study 4705 (lower 95% CI boundary of –0.40 litres x hours). Both studies 4334 and 4073 reported statistically significant improvements in FEV_1 AUC for mometasone/formoterol compared with placebo.
- The percentage of patients experiencing a severe asthma exacerbation was not statistically significantly different between mometasone/formoterol and fluticasone/salmeterol in study 4705 (19.4% versus 16.5%, respectively), or in study 4139 for both moderate- and high-dose treatment groups (23.4% versus 17.5% and 32.2% versus 27.7%, respectively). The frequency of severe asthma exacerbations was statistically significantly lower for mometasone/formoterol-treated patients compared with placebo in studies 4334 and 4073.
- There was no statistically significant difference in quality of life between mometasone/formoterol and fluticasone/salmeterol in study 4705, as measured by the AQLQ(S). Compared with placebo, mometasone/formoterol resulted in statistically significant improvements in quality of life as measured by the AQLQ(S) in studies 4334 and 4073, but the clinical importance of the differences was uncertain. Quality of life was not investigated in study 4139.
- There were no statistically significant differences between mometasone/formoterol and fluticasone/salmeterol in asthma symptoms, or asthma symptom-free days, nights, or days and nights combined, in both studies 4705 and 4139.
- The reduction in the use of rescue medication was statistically significantly greater for patients randomized to fluticasone/salmeterol compared with mometasone/formoterol in study 4705, and numerically greater for patients randomized to both moderate- and high-dose fluticasone/salmeterol compared with equivalent doses of mometasone/formoterol in study 4139.

© 2011 CADTH

Harms (Safety and Tolerability)

- There were no statistically significant differences in the frequency of serious adverse events or adverse events between mometasone/formoterol and fluticasone/salmeterol, or between mometasone/formoterol and placebo in any of the reviewed trials.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-comparison analysis of mometasone/formoterol with fluticasone/salmeterol and budesonide/formoterol based on the assumption of similar efficacy and harms. Two head-to-head studies (4705 and 4139) comparing mometasone/formoterol with fluticasone/salmeterol were used to support their assumption of similar efficacy and harms. As there were no head-to-head trials available comparing mometasone/formoterol and budesonide/formoterol, the manufacturer conducted a mixed treatment comparison meta-analysis to support its claims of equivalent efficacy for outcomes of symptom-free days and morning peak expiratory flow. However, in the absence of head-to-head trials comparing mometasone/formoterol with budesonide/formoterol, it is difficult to establish dose equivalence.

Based on recommended maintenance doses, the daily cost of mometasone/formoterol ($2.23 to $3.43) is less expensive than fluticasone/salmeterol ($2.68 to $4.56) but more expensive than budesonide/formoterol ($0.51 to $2.68). The cost of mometasone/formoterol is more expensive than monotherapy alternatives.

Patient Input Information:

The following is a summary of information provided by one patient group that responded to the CDR Call for Patient Input:

- Outcomes of importance to patients include quality of life, reduction in the frequency of exacerbations, and maintenance or improvement of lung function.
- Additional options for controller medications were said to be desirable, since it was noted that many patients with asthma try three or more controller medications before finding one that is both effective and tolerable.
- Patients are willing to accept short-term adverse effects of controller medications (e.g., thrush, taste effects, soreness, hoarseness, and dryness), as long as medications are effective.

Other Discussion Points:

- The Committee noted that mometasone is not marketed in Canada as a single-agent inhalation product. Thus, titration to optimal mometasone dosage, prior to the use of combination mometasone/formoterol is not possible. Given safety concerns regarding the use of LABAs for the treatment of asthma, the Committee expressed concern that the efficacy and safety of mometasone/formoterol compared with monotherapy with an inhaled corticosteroid marketed in Canada has not been demonstrated.

© 2011 CADTH

CEDAC Members:
Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. James Silvius.

July 20, 2011 Meeting

Regrets:
None

Conflicts of Interest:
None

September 21, 2011 Meeting

Regrets:
Two CEDAC members did not attend.

Conflicts of Interest:
None

About this Document:
CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer.

© 2011 CADTH