Canadian Expert Drug Advisory Committee
Final Recommendation – Plain Language Version

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 Zenhale, which is also called mometasone furoate/formoterol fumarate dihydrate inhalation aerosol, not be listed by Canada's publicly funded drug plans for the maintenance treatment of asthma.

Reasons for the Recommendation:
1. The Committee could not be certain how the benefit of Zenhale compared with other treatments. The only study looking at the effectiveness of Zenhale compared with fluticasone/salmeterol (also called Advair) in asthma (study 4705) had some shortcomings because it was stopped early at 12 weeks, and allowed patients to know which treatment they were getting. Also, for the primary outcome (lung function), it was uncertain if the size of the difference chosen by the manufacturer to test whether Zenhale was not worse than fluticasone/salmeterol would be important to patients.
2. There are no medical studies in patients with asthma that compare the effectiveness and safety of Zenhale with a single-ingredient corticosteroid inhaler that is marketed in Canada.

Background:
Zenhale is a combination product inhaler. Zenhale contains two medicines, mometasone furoate and formoterol fumarate dihydrate:
- Mometasone furoate is a corticosteroid. Corticosteroids are used to prevent asthma attacks because they have an anti-inflammatory effect (reduce swelling and irritation in the walls of the small air passages of the lungs, easing breathing problems).
- Formoterol fumarate dihydrate is a long-acting beta-agonist (a bronchodilator). Bronchodilators help the airways in the lungs to stay open; they make breathing easier by relaxing muscle spasms in the air passages of the lungs. The effects last for 12 hours.

Zenhale is approved by Health Canada for maintenance treatment of asthma, in adults and children aged 12 years 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 medication in the following dose combinations of mometasone/formoterol, respectively, per inhalation: 50 mcg/5 mcg, 100 mcg/5 mcg, and 200 mcg/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 mcg/20 mcg (given as two inhalations of Zenhale 200 mcg/5 mcg twice daily) for patients aged 12 years and older.

Summary of CEDAC Considerations:
To make their decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of Zenhale and a review of economic information prepared by the manufacturer of Zenhale. Also, CEDAC considered information that patient groups submitted about outcomes and issues important to patients who have the condition for which the drug is indicated, or who might use the drug.

Clinical Trials
CEDAC reviewed four medical studies of patients aged 12 years and older with asthma, and a minimum 12-week use of inhaled corticosteroids (low dose in study 4073, medium dose in studies 4705 and 4334, and medium or high dose in study 4139) with or without a long-acting beta-agonist.

- Study 4705 included 722 patients. In this study, patients were given either Zenhale 200 mcg/10 mcg twice daily or fluticasone/salmeterol 250 mcg/50 mcg twice daily. Patients were aware of which treatment they were receiving. Despite a planned 52-week duration, the manufacturer stopped the study after 12 weeks.
- Study 4139 included 404 patients. In this study, patients were provided with treatment based upon their most recent dose of inhaled corticosteroids. Patients were aware of which treatment they were receiving. Patients using medium doses of inhaled corticosteroids were given either Zenhale 200 mcg/10 mcg or fluticasone/salmeterol 250 mcg/50 mcg twice daily. Patients on high doses of inhaled corticosteroids were given either Zenhale 400 mcg/10 mcg or fluticasone/salmeterol 500 mcg/50 mcg twice daily. The study lasted 52 weeks.
- Study 4334 included 781 patients. Patients were given one of four different treatments (all twice daily): Zenhale 200 mcg/10 mcg, mometasone 200 mcg, formoterol 10 mcg, or placebo (an inhalation containing no active medication) for 26 weeks. Neither the patients nor the treating doctor knew which treatment the patient was receiving.
- Study 4073 included 746 patients. Patients were given one of four different treatments: Zenhale 100 mcg/10 mcg, mometasone 100 mcg, formoterol 10 mcg, or placebo (all twice daily) for 26 weeks. Neither the patients nor the treating doctor knew which treatment the patient was receiving.

All studies, except study 4139, included two to three weeks of treatment with mometasone only before the patients were given their study medication. All studies allowed the use of short-acting beta-agonists (e.g., Ventolin) on an “as-needed” basis. However, if patients needed to take steroids by mouth or by injection, they had to stop taking part in the study.

The early stopping of study 4705 was considered a shortcoming. Approximately 15% of patients stopped taking part during study 4139, regardless of which treatment the patient was getting. In the studies with placebo, approximately 29% of patients stopped taking part during the study; the percentage was higher in the placebo groups compared with the Zenhale groups in both studies 4334 and 4073 (39% versus 18%, and 38% versus 20%, respectively).

Outcomes

Outcomes were defined in advance in the CDR systematic review protocol. Of these, the Committee discussed the following: frequency of exacerbations (worsenings), asthma symptoms, quality of life, rescue medication use (use of other treatments if the study medication was not working), and change in lung function tests.

- The main purpose of study 4705 was to look at the change in lung function from study start, as measured by the forced expiratory volume in one second (FEV_1). Zenhale would be considered not worse than fluticasone/salmeterol if the average change in the FEV_1 for Zenhale patients was not more than 1.5 litres x hours lower than the average for fluticasone/salmeterol patients.
- Study 4139 was a safety study and the main purpose was to measure the frequency of side effects.
- The main purposes of studies 4334 and 4073 were to measure both the length of time to the first worsening of asthma, and the change in lung function from study start, as measured by the FEV_1.

The Asthma Quality of Life Questionnaire with Standardized activities [AQLQ(S)] scores items in four areas (activity limitation, symptoms, emotional function, and environmental stimuli) from 1 to 7, with lower scores being linked to a worse condition. The smallest change in the AQLQ-S that is important to patients varies from 0.5 to 1.0.

Results

The Committee focused its discussion on comparisons between Zenhale and either fluticasone/salmeterol or placebo because mometasone is not marketed in Canada as a single-ingredient inhaler and because treatment with a long-acting beta-agonist alone is not considered an option for asthma therapy, due to safety concerns.

Efficacy or Effectiveness

- In study 4705 and study 4139, Zenhale improved lung function about the same amount as fluticasone/salmeterol. In study 4705, Zenhale was not worse than fluticasone/salmeterol in terms of the improvement in FEV_1 compared with that at the start of the study. Both studies 4334 and 4073 showed that Zenhale was better than placebo in terms of improving the FEV_1.
- The percentage of patients who had severe worsening of asthma was about the same regardless of whether the patient was on Zenhale or on fluticasone/salmeterol in both study 4705 (19.4% versus 16.5%, respectively) and study 4139 (for moderate- as well as high-dose treatment groups, 23.4% versus 17.5%, and 32.2% versus 27.7%, respectively). Severe worsening of asthma occurred less often in Zenhale-treated patients compared with those treated with placebo, in studies 4334 and 4073.
- There was no difference in quality of life between Zenhale and fluticasone/salmeterol in study 4705, as measured by the AQLQ(S). Compared with placebo, patients on Zenhale had more improvement in quality of life as measured by the AQLQ(S) in studies 4334 and 4073, but it is not known how important this difference would be for patients. Quality of life was not measured in study 4139.
- There were no differences between Zenhale and fluticasone/salmeterol in terms of asthma symptoms, or asthma symptom–free days, nights, or days and nights combined, in both studies 4705 and 4139.

- The decrease in the use of rescue medication was greater for patients taking fluticasone/salmeterol compared with Zenhale in study 4705. In study 4139, the decrease in rescue medication was also greater for patients taking both the moderate- and high-dose fluticasone/salmeterol compared with Zenhale groups, but the difference between the treatments was small enough to have been due to chance.

Harms (Safety and Tolerability)

- The frequency of serious side effects and side effects in general was not much different between Zenhale and fluticasone/salmeterol, or between Zenhale and placebo in any of the reviewed studies.

Cost and Cost-Effectiveness

The manufacturer submitted economic information to compare Zenhale with fluticasone/salmeterol and budesonide/formoterol (also called Symbicort) based on the assumption of similar effectiveness and harms. Two studies (4705 and 4139) comparing Zenhale with fluticasone/salmeterol were used to support the manufacturer's assumption of similar effectiveness and harms. As there were no studies available comparing Zenhale with budesonide/formoterol, the manufacturer used the combination of data from a number of studies to support its claims of similar effectiveness based on the outcomes of symptom-free days, and morning peak expiratory flow. However, because there are no studies comparing Zenhale with budesonide/formoterol, it is difficult to say what dose of Zenhale corresponds to what dose of budesonide/formoterol.

Based on recommended maintenance doses, the daily cost of Zenhale ($2.23 to $3.43) is less than fluticasone/salmeterol ($2.68 to $4.56), but higher than budesonide/formoterol ($0.51 to $2.68). The cost of Zenhale is higher than single-ingredient 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, decrease in the number of asthma worsenings, and maintenance or improvement of lung function.
- The patient group said additional options for controller medications are desirable, as it was noted that many patients with asthma try three or more controller medications before finding one that works and is tolerable.
- Patients are willing to accept short-term side effects of controller medications (e.g., thrush [yeast infection of the throat], taste effects, soreness, hoarseness, and dryness) as long as medications are effective.

Other Discussion Points:

- The Committee noted that a mometasone (single-ingredient) inhaler is not marketed in Canada. Thus, it is not possible to make sure that a patient is on the best mometasone dosage for him or her individually, prior to switching to the combination product (Zenhale). Given safety concerns regarding the use of long-acting beta-agonists for the treatment of asthma, the Committee was concerned that the effectiveness and safety of Zenhale compared with a single-ingredient corticosteroid inhaler marketed in Canada has not been shown.

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
The information contained within this plain language version of the Canadian Expert Drug Advisory Committee (CEDAC) Recommendation about this drug is based on the information found within the corresponding technical version of the CEDAC Recommendation.

In making its recommendation, CEDAC considered the best clinical and pharmacoeconomic evidence available, up to that time. Health care professionals and those requiring more detailed information are advised to refer to the technical version available in the CDR Drug Database on the CADTH website (www.cadth.ca).

Background on CEDAC
CEDAC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). The committee is made up of drug evaluation experts and public members. CEDAC provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans; however, the individual drug plans make their own decision about whether or not to cover a drug.

In making its recommendations, CEDAC decides if the drug under review ought to be covered by the participating public drug plans based on an evidence-informed review of the medication's effectiveness and safety, and based on an assessment of its cost-effectiveness in comparison with other available treatments. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.
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The manufacturer has reviewed this document and has not requested the deletion of any confidential information.