CDEC FINAL RECOMMENDATION

MOMETASONE FUROATE/FORMOTEROL FUMARATE DIHYDRATE INHALATION AEROSOL – REQUEST FOR ADVICE

(Zenhale – Merck Canada Inc.)

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

This recommendation supersedes the Canadian Expert Drug Advisory Committee (CEDAC) recommendation for this drug and indication dated September 28, 2011.

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that mometasone furoate/formoterol fumarate dihydrate (Zenhale) be listed with the following condition:

- List in a manner similar to other combination inhaled corticosteroid/long-acting beta agonists (ICS/LABAs).

Reasons for the Recommendation:

1. Three randomized controlled trials (RCTs) demonstrated that combination use of mometasone/formoterol was more efficacious than mometasone monotherapy for improving lung function in patients with asthma, as measured by the forced expiratory volume in one second (FEV_1).
2. The individual components of the mometasone/formoterol combination product have been approved by Health Canada for the treatment of asthma. The cost of the mometasone/formoterol combination product is comparable to the cost of the individual components.

Background:
Zenhale is a fixed-dose combination of an ICS (mometasone furoate) and a 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 who have reversible obstructive airway disease, but for whom the asthma cannot be adequately controlled on asthma controller medications.

Zenhale is a metered dose inhaler available in the following dose combinations of mometasone and formoterol respectively, per actuation: 50 mcg / 5 mcg, 100 mcg / 5 mcg, and 200 mcg / 5 mcg. The recommended dose is two inhalations twice daily (morning and evening), up to a maximum of 800 mcg / 20 mcg for patients 12 years of age and older.

Submission History:
The Canadian Expert Drug Advisory Committee (CEDAC) previously reviewed mometasone/formoterol for the same indication and the drug combination received a recommendation of "do not list" (see Notice of CEDAC Final Recommendation, September 28, 2011). The reasons for the recommendation were:

1. The Committee considered the comparative clinical benefit of mometasone/formoterol to be uncertain. The only 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, high frequency of non-completion, 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 ICS monotherapy marketed in Canada.

The Final CEDAC Recommendation further noted, that despite two RCTs comparing mometasone/formoterol with mometasone monotherapy, the Committee focused its discussion on comparisons between mometasone/formoterol and either fluticasone/salmeterol or placebo because mometasone monotherapy for inhalation was not marketed in Canada.

The Common Drug Review (CDR) participating jurisdictions submitted a Request for Advice for mometasone/formoterol, for the following reasons:

- Mometasone monotherapy for inhalation (Asmanex) is now marketed in Canada, and the Final CDEC Recommendation recommended that Asmanex be listed for the prophylactic management of steroid-responsive bronchial asthma (see Notice of CEDAC Final Recommendation, May 16, 2012).
- Formoterol, a LABA, is available as an individual product for inhalation and is reimbursed by a number of jurisdictions for the treatment of asthma in patients inadequately controlled on optimal doses of an ICS.
- The daily cost of Zenhale is similar to, or less costly than, inhaled mometasone plus formoterol given separately.

Summary of CDEC Considerations:
In addition to the information prepared by CDR for the original consideration of mometasone/formoterol, the Committee considered a clinical brief that included three additional double-blind RCTs comparing an ICS with or without formoterol.

Patient Input Information
The following is a summary of information provided by one patient group that responded to the CDR Call for Patient Input for the original CDR review of mometasone/formoterol:

- Outcomes of importance to patients include quality of life, reduction in the frequency of exacerbations, and maintenance or improvement of lung function.
- Having additional options for controller medications was 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., oral thrush, taste effects, throat soreness, hoarseness, and dryness), as long as medications are effective.

Clinical Trials

The three RCTs included in the clinical brief enrolled patients 12 years and older who have asthma and who were using an ICS for at least 12-weeks, with or without a LABA.

- Study 4334 (N = 781) randomized patients to one of four treatment groups: mometasone/formoterol 200 mcg / 10 mcg (moderate dose), mometasone 200 mcg (moderate dose), formoterol 10 mcg, or placebo (all twice daily) for 26 weeks.
- Study 4073 (N = 746) randomized patients to one of four treatment groups: mometasone/formoterol 100 mcg / 10 mcg (low dose), mometasone 100 mcg (low dose), formoterol 10 mcg, or placebo (all twice daily) for 26 weeks.
- Study 4431 (N = 728) randomized patients to one of three treatment groups: mometasone/formoterol 200 mcg / 10 mcg (moderate dose), mometasone/formoterol 400 mcg / 10 mcg (high dose), mometasone 400 mcg (high dose) (all twice daily) for 12 weeks.

All studies included a two- to three-week open-label run-in period where patients received mometasone monotherapy before randomization. All trials permitted the use of short-acting beta-agonists as rescue medication on an as-needed basis. However, systemic steroid use resulted in patients' early termination from trials.

The withdrawal rates were similar in the mometasone/formoterol groups (11% to 20%) compared with the mometasone monotherapy groups (14% to 22%).

Outcomes

Outcomes were defined a priori in the CDR briefing document. Of these, the Committee discussed the following: frequency of exacerbations, asthma symptoms, quality of life, rescue medication use, changes in lung function tests, adverse events, and withdrawals due to adverse events.

Change from baseline in lung function, as measured by the FEV_1 area under curve (AUC), was a primary outcome in all of the included trials. Time to first asthma deterioration was included as a co-primary outcome in studies 4334 and 4073. Secondary outcomes included the standardized Asthma Quality of Life Questionnaire (AQLQ[S]), the Asthma Control Questionnaire, use of rescue medication, nocturnal awakenings requiring rescue medication, and asthma exacerbations.

The AQLQ(S) scores items in four domains (activity limitation, symptoms, emotional function, and environmental stimuli) from one to seven, with lower scores indicating greater impairment. The reported minimal clinically important difference for the AQLQ(S) varies from 0.5 to 1.0.

Results

Efficacy or Effectiveness

- All three trials reported statistically significant improvements in FEV_1 AUC for mometasone/formoterol compared with mometasone monotherapy.
- The percentage of patients experiencing a severe asthma exacerbation was statistically significantly lower with low-dose mometasone/formoterol than low-dose mometasone monotherapy in study 4073 (16.5% versus 28.2%; *P* = 0.006). However, the percentage of patients experiencing a severe asthma exacerbation was not statistically significantly

different between moderate-dose mometasone/formoterol and moderate-dose mometasone monotherapy in study 4334 (30.4% versus 33.9%; *P* = 0.56). In study 4431, the percentage of patients experiencing a severe asthma exacerbation was statistically significantly lower in moderate-dose mometasone/formoterol than high-dose mometasone monotherapy (12.4% versus 18.3%; *P* = 0.038), but no statistically significant difference was observed in high-dose mometasone/formoterol compared with high-dose mometasone monotherapy (12.2% versus 18.3%; *P* = 0.053).

- None of the three studies reported a statistically significant difference in quality of life between mometasone/formoterol and mometasone monotherapy as measured by the AQLQ(S), except between moderate-dose mometasone/formoterol and high-dose mometasone monotherapy, which was in favour of mometasone/formoterol (*P* = 0.017).
- A moderate dose of mometasone/formoterol was favoured compared with a high-dose mometasone monotherapy in study 4431 (*P* = 0.016) for asthma symptoms (measured using the Asthma Control Questionnaire); however, there were no statistically significant differences between mometasone/formoterol and mometasone monotherapy in the other studies.
- There were no statistically significant differences in the daily use of rescue medication (i.e., short-acting beta-agonists) for mometasone/formoterol compared with mometasone monotherapy. Nocturnal awakenings requiring the use of rescue medication were significantly lower in both the high- and medium-dose mometasone/formoterol groups compared with mometasone monotherapy in study 4431; however, there were no significant differences between mometasone/formoterol and mometasone monotherapy in studies 4073 and 4334.

Harms (Safety and Tolerability)

- The frequency of serious adverse events and total adverse events was similar in the mometasone/formoterol and mometasone monotherapy groups.

Cost and Cost-Effectiveness

When considering similar recommended maintenance doses, the cost of mometasone/formoterol (2 x 100 mcg / 5 mcg to 2 x 200 mcg / 5 mcg twice daily; $2.83 to $3.42) is similar to the cost of the individual drugs (mometasone plus formoterol) taken in combination (200 mcg plus 12 mcg twice daily to 400 mcg plus 12 mcg twice daily; $2.66 to $3.84). When compared with other combination products, the daily cost of mometasone/formoterol ($2.23 to $3.42) is less than fluticasone/salmeterol ($2.68 to $4.56), but more than budesonide/formoterol ($0.53 to $2.76).

Other Discussion Points:

The Committee noted the following:

- Only one RCT, Study 4705, which had several limitations, compared the efficacy of mometasone/formoterol with another ICS/LABA (fluticasone/salmeterol) in asthma.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

November 21, 2012 Meeting

Regrets:
None

Conflicts of Interest:
None

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

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