# CDEC FINAL RECOMMENDATION

## AZELASTINE/FLUTICASONE PROPIONATE
## (Dymista — Meda Pharmaceuticals Ltd.)
## Indication: Seasonal Allergic Rhinitis

**Recommendation:**
The Canadian Drug Expert Committee (CDEC) recommends that azelastine hydrochloride/ fluticasone propionate (AZE/FP) not be listed for the symptomatic treatment of moderate-to-severe seasonal allergic rhinitis (SAR) and associated ocular symptoms in adults and adolescents aged 12 years and older for whom monotherapy with either antihistamines or intranasal corticosteroids is not considered sufficient.

**Reasons for the Recommendation:**

1. Four randomized controlled trials (RCTs) (MP4002, MP4004, MP4006, and MP4001) demonstrated that AZE/FP provides statistically superior relief of nasal symptoms (reflective total nasal symptom score [rTNSS]), ocular symptoms (reflective total ocular symptom score [rTOSS]), and quality of life (Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ]) compared with placebo in patients with SAR; however, the comparative clinical benefit of AZE/FP versus fluticasone propionate alone is uncertain.
2. Although AZE/FP was statistically superior to fluticasone propionate for improving nasal symptoms, the magnitude of improvement (0.64 to 0.99 points on the rTNSS in three trials [MP4002, MP4004, and MP4006]) was small and of uncertain clinical significance. In addition, AZE/FP was not consistently shown to be statistically superior to fluticasone propionate for improving ocular symptoms or quality of life.

**Background:**
AZE/FP is indicated for the treatment of moderate-to-severe SAR and associated ocular symptoms in adults and adolescents aged 12 years and older for whom monotherapy with either antihistamines or intranasal corticosteroids is not considered sufficient. AZE/FP is a nasal spray suspension containing 0.1% azelastine hydrochloride (w/w) and 0.037% fluticasone propionate (w/w). Each spray contains 138 mcg azelastine hydrochloride and 50 mcg fluticasone propionate. The recommended dose of AZE/FP for patients aged 12 years and older is one spray in each nostril twice daily (morning and evening) for a total daily dose of 548 mcg azelastine hydrochloride and 200 mcg fluticasone propionate.

**Summary of Canadian Drug Expert Committee Considerations**
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of AZE/FP, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to those with SAR.

### *Patient Input Information*

The following is a summary of information provided by one patient group that responded to the CDR call for patient input:

- Patients reported a persistent year-round impact of SAR on day-to-day quality of life. Symptoms include nasal congestion, moderate or severe runny nose, itchy nose, sneezing, itchy eyes, watery eyes, and eye redness. Patients can experience multiple allergic rhinitis episodes annually, each lasting two weeks on average.
- Patients noted a substantial impact of allergy symptoms on sleep, daily activities (including leisure and sport), and workplace productivity. Many patients had multiple annual visits to health care providers, were dissatisfied with their current medications, and found it challenging to obtain a referral to an allergist from their family physicians.
- Currently available treatments include oral antihistamines, intranasal corticosteroids, antihistamine drops, and subcutaneous or sublingual immunotherapy. A combination of intranasal corticosteroids, oral antihistamines and eye drops is typically used. Approximately half of the surveyed patients were very satisfied or somewhat satisfied with the effectiveness of their current treatment. For those who are not satisfied, additional treatment is needed to relieve nasal and ocular symptoms.

### *Clinical Trials*

The CDR systematic review included four studies (MP4002 [N = 832], MP4004 [N = 779], MP4006 [N = 1,801], and MP4001 [N = 610]), which were all similar in design: phase 3, randomized, double-blind, placebo-controlled, parallel group, 14-day studies of patients with moderate-to-severe SAR. The objective of all included studies was to test the superiority of AZE/FP over each individual component alone and placebo for the improvement of symptoms of SAR. Patients were randomized (1:1:1:1) to receive one spray per nostril twice daily (morning and evening) of AZE/FP, azelastine, fluticasone propionate, or placebo.

### *Outcomes*

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Total nasal symptom score (TNSS) — a composite end point of four symptoms (running nose, sneezing, itchy nose, and nasal congestion). The combined TNSS has a maximum score of 24 points. The minimal clinically important difference (MCID) has not been established. The TNSS was evaluated as change from baseline in 12-hour rTNSS and instantaneous score (iTNSS).
- Total ocular symptom score (TOSS) — a composite end point of three symptoms (itchy eyes, watery eyes, and eye redness). The combined TOSS has a maximum score of 18 points. The MCID has not been established. The TOSS was evaluated as change from baseline in 12-hour rTOSS and iTOSS.
- RQLQ — a 28-item questionnaire with seven domains (Activities, Sleep, Non-nose/Eye Symptoms, Practical Problems, Nasal Symptoms, Eye Symptoms, and Emotional) that are rated on a 7-point scale (0 to 6). The MCID is considered to be 0.5 points.
- Onset of action — change from baseline in iTNSS over a four-hour period following the initial administration of the study drug.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The primary efficacy outcome in all four studies was the change from baseline in rTNSS for the entire 14-day study period.

***Efficacy***

- Treatment with AZE/FP for 14 days was associated with a statistically significant improvement in overall rTNSS compared with azelastine ($P < 0.05$) and fluticasone propionate ($P < 0.05$) alone. The relative benefit of AZE/FP ranged from 0.71 to 2.06 compared with azelastine and from 0.64 to 1.47 compared with fluticasone propionate.
- AZE/FP was consistently better than azelastine throughout the treatment period, whereas the relative benefit of AZE/FP over fluticasone propionate appeared to be driven by a greater improvement within the first few days of treatment.
- The onset of action for AZE/FP was not statistically significantly faster than azelastine (MP4002, MP4004, and MP4006) or fluticasone propionate (MP4002 and MP4004).
- For overall rTOSS, the effect of AZE/FP was not statistically significantly different compared with azelastine in any study. There was no statistically significant difference compared with fluticasone propionate in MP4002 and MP4006; however, there was a statistically significant difference between AZE/FP and fluticasone propionate in MP4004 ($P = 0.009$) and MP4001 ($P = 0.002$).
- In each of the included studies, AZE/FP demonstrated a statistically significant improvement in RQLQ total scores compared with azelastine, but not with fluticasone propionate. The difference in the overall RQLQ score between AZE/FP and azelastine ranged from 0.17 to 0.43.

***Harms (Safety and Tolerability)***

- Serious adverse events were rare across the included studies and were reported for only two AZE/FP-treated patients, one placebo-treated patient, and no patients in either the azelastine or fluticasone propionate treatment groups.
- The proportion of patients who experienced at least one adverse event was reported as follows: AZE/FP 14.5% to 19%; azelastine 12.5% to 18.0%; fluticasone propionate 12.2% to 15.5%); and placebo 10.0% to 12.2%.
- The proportion of patients who withdrew as a result of adverse events was reported as follows: AZE/FP 0.7% to 1.9%; azelastine 0.5% to 1.3%; fluticasone propionate 0% to 0.7%; and placebo 0.5% to 1.1%.

***Cost and Cost-Effectiveness***

The manufacturer submitted a cost-utility analysis comparing AZE/FP with fluticasone propionate, azelastine, and placebo in the treatment of SAR from a health care system perspective. The time horizon was assumed to be 14 days, based on the duration of MP4001. The cost-utility analysis was based on a trial-based model that estimated, on the basis of daily symptom scores from MP4001, the differences between AZE/FP, fluticasone propionate, azelastine, and placebo in terms of mean costs and effectiveness. The effectiveness is expressed as quality-adjusted life-hours (QALHs), which are subsequently converted to incremental quality-adjusted life-years (QALYs). The manufacturer reported that, based on a sequential analysis, fluticasone propionate produced an incremental cost-utility ratio (ICUR) of $12,223 per QALY compared with placebo; azelastine was dominated by fluticasone propionate (more costly, fewer QALY gains); and AZE/FP had an ICUR of 70,957 per QALY compared with fluticasone propionate.

CDR identified several limitations relating to the manufacturer's model:

- Assessment of comparative efficacy: data for AZE/FP were based on MP4001 instead of a meta-analysis of the four available studies (MP4001, MP4002, MP4004, and MP4006).
- Although patients with severe SAR require between two and four weeks of treatment, the model was based on a short time horizon (14 days).
- Adjustment of QALHs was based on gender and age, while treatment groups were comparable with regard to demographic and baseline clinical characteristics in the clinical trials.
- Inappropriate methodology was used to incorporate utility decrements associated with adverse events.
- Costs of co-medications (e.g., oral antihistamines and eye drops) and physician visits were not included in the base-case analysis.

Due to structural limitations of the submitted model, CDR was unable to conduct sensitivity analyses on the time horizon, the impact of adverse events on quality of life, the impact of adjusting QALHs based on age or gender separate from each other, and the impact of including the costs of co-medications and physician visits on model results. Eliminating an adjustment to QALH based on both gender and age increased the ICUR for AZE/FP compared with fluticasone propionate from $70,957 to $122,405 per QALY. When the efficacy data from the meta-analysis of MP4001, MP4002, MP4004, and MP4006 were used, the ICUR for AZE/FP compared with fluticasone propionate increased to $116,575 per QALY. The CDR most-likely scenario, based on pooled efficacy data from MP4001, MP4002, MP4004, and MP4006 and excluding the QALH adjustments based on age and gender, found that the ICUR of AZE/FP compared with fluticasone propionate was $194,592 per QALY. A price reduction of 55% would reduce the ICUR of AZE/FP compared with fluticasone propionate to $51,072 per QALY.

AZE/FP was submitted at a price of $[redacted] per spray ($[redacted] daily). Fluticasone propionate is available as a generic at a daily cost of $0.7323 to $1.4647. Azelastine is not currently approved for use as monotherapy in Canada.

**Other Discussion Points:**

CDEC noted the following:

- The included RCTs did not clearly define a study group that met the criteria specified in the Health Canada–approved indication (i.e., those for whom monotherapy with either antihistamines or intranasal corticosteroids is not considered sufficient). Supplemental information submitted by the manufacturer suggested that up to 20% of patients may have had inadequate response to intranasal corticosteroids and up to 40% of patients may have had inadequate response to antihistamines.
- The Health Canada review included a meta-analysis of rTNSS based on age subgroups using pooled data, which showed that AZE/FP did not demonstrate a statistically significant difference versus fluticasone in patients between 12 and 17 years of age. However, the clinical expert consulted by CDR suggested that the efficacy of AZE/FP would not be expected to differ by age, but the effectiveness could be influenced by lower compliance in children.

**CDEC Members:**
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

**May 20-21, 2015 Meeting**

**Regrets:**
None

**Conflicts of Interest:**
None

**About this Document:**
CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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