Common Drug Review
Pharmacoeconomic Review Report

May 2016

Drug	azelastine hydrochloride and fluticasone propionate nasal spray (AZE/FP)
Indication	The symptomatic treatment of moderate-to-severe seasonal allergic rhinitis and associated ocular symptoms in adults and adolescents aged 12 and older for whom monotherapy with either antihistamines or intranasal corticosteroids is not considered sufficient.
Listing request	As per indication
Manufacturer	Meda Pharmaceuticals Ltd.

The azelastine hydrochloride/fluticasone propionate nasal spray (Dymista) CADTH Common Drug Review Pharmacoeconomic Report was prepared using PharmaStat data from IMS Health Canada Inc. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in allergy and immunology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update – Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

AE	adverse event
AZE	azelastine hydrochloride
AZE/FP	azelastine hydrochloride and fluticasone propionate fixed-dose combination
CDR	CADTH Common Drug Review
CUA	cost-utility analysis
EQ-5D	EuroQol 5-Dimensions Questionnaire
FDC	fixed-dose combination
FP	fluticasone propionate
ICUR	incremental cost-utility ratio
QALH	quality-adjusted life-hour
QALY	quality-adjusted life-year
QoL	quality of life
SAR	seasonal allergic rhinitis
TNSS	total nasal symptom score
TOSS	total ocular symptom score

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Azelastine hydrochloride/fluticasone propionate (Dymista) nasal spray
Study Question	"From the perspective of CDR, what is the incremental cost-effectiveness of AZE/FP nasal spray (Dymista) compared with FP, AZE, and placebo in the treatment of moderate-to-severe SAR in Canada?"
Type of Economic Evaluation	Cost-utility analysis
Target Population	Moderate-to-severe SAR patients aged 12 years and older
Treatment	One actuation of AZE/FP nasal spray in each nostril twice daily (morning and evening) for 14 days
Outcome(s)	QALHs QALYs
Comparator(s)	• FP • AZE • Placebo
Perspective	Health care payer
Time Horizon	14 days
Results for Base Case	Based on the manufacturer's sequential analysis: • FP had an ICUR of $12,223 per QALY compared with placebo • AZE was dominated by FP (more costly, fewer QALY gains) • AZE/FP had an ICUR of $70,957 per QALY compared with FP ($31,936 vs. placebo)
Key Limitations	CDR noted several limitations with the manufacturer's model: • Uncertainty regarding the sources for efficacy estimates: ○ The manufacturer's reference case is based on the results of study MP4001 only. The treatment effect of AZE/FP was relatively greater in study MP4001 compared with others (MP4002, MP4004, and MP4006). Using pooled estimates from the 4 trials would have been a more conservative approach. • Short duration of treatment (14 days), although patients with severe SAR require between 2 and 4 weeks of treatment • Inappropriate methodology used to incorporate utility decrements associated with AEs • QALHs were adjusted based on gender and age despite clinical expert opinion indicating no perceived impact on efficacy of treatments in SAR • Costs of co-medications and physician visits were not included in the base-case analysis. However, non-Canadian estimates were in the sensitivity analysis.
CDR Estimate(s)	Due to structural limitations of the submitted model, CDR was unable to conduct the following sensitivity analyses: • Varying the treatment duration beyond the manufacturer's 14-day time horizon • Assessing the impact of AEs on quality of life in patients with SAR • Assessing the impact of including the costs of co-medications and physician visits on results • Structural limitations with the model did not allow CDR to assess the impact of adjusting the QALHs on age in separation from gender.

[redacted]	The CDR multi-way reanalysis used pooled efficacy data from MP4001, MP4002, MP4004, and MP4006 and excluded adjustment of QALH based on gender and age: • ICUR of AZE/FP vs. placebo: $40,861 per QALY • ICUR of AZE/FP vs. FP: $194,592 per QALY.

AE = adverse event; AZE = azelastine hydrochloride; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; CDR = CADTH Common Drug Review; FP = fluticasone propionate; ICUR = incremental cost-utility ratio; QALH = quality-adjusted life-hour; QALY = quality-adjusted life-year; SAR = seasonal allergic rhinitis; vs. = versus.

EXECUTIVE SUMMARY

Background

Dymista (azelastine hydrochloride/fluticasone propionate) is a fixed-dose combination (FDC) of an antihistamine (azelastine hydrochloride [AZE]) and a corticosteroid (fluticasone propionate [FP]) indicated 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.[1] It is available as a nasal spray containing 137 mcg of azelastine hydrochloride and 50 mcg of fluticasone propionate per metered spray.[1] The recommended dose is one actuation in each nostril twice daily. The manufacturer submitted a confidential price of $[redacted] per spray ($[redacted] daily).

The manufacturer has requested that AZE/FP be listed as per Health Canada indication.[2]

The manufacturer submitted a cost-utility analysis comparing AZE/FP with FP, AZE, and placebo in the treatment of SAR using data from study MP-4001.[3] The time horizon was assumed to be 14 days, based on trial duration of study MP-4001 using the health care system perspective. The cost-utility analysis was based on a trial-based model that estimated, on the basis of daily symptom scores from study MP4001, the differences between AZE/FP, FP, AZE, 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).

Results of the reference case analysis showed FP to be the least costly treatment ($10.25) while AZE/FP was the most costly ($[redacted]). The manufacturer reported that, based on a sequential analysis, FP produced an ICUR of $12,223 per QALY compared with placebo, AZE was dominated by FP (more costly, fewer QALY gains), and AZE/FP had an ICUR of 70,957 per QALY compared with FP.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several limitations with the submitted economic analysis. A key limitation was that the comparative efficacy data for AZE/FP were based on study MP4001 and not a meta-analysis of the four available studies (MP4001, MP4002, MP4004, and MP4006). A pooled analysis of the four studies was available within the model, but wasn't reported in the manufacturer's pharmacoeconomic report. Other limitations are as follows: the time horizon for the analysis was 14 days, although expert opinion indicated patients with severe SAR require between two and four weeks of treatment; 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; and finally, the manufacturer's rationale for the adjustment of QALHs based on gender and age was unclear. Due to structural limitations of the submitted model, CDR was unable to conduct sensitivity analyses varying the treatment duration beyond the manufacturer's 14 days, the impact of adverse events on quality of life in patients with SAR, the impact of adjusting QALHs based on age or gender in detachment of each other, and 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 FP from $70,957 to $122,405 per QALY. When the efficacy data from meta-analysis of MP4001, MP4002, MP4004, and MP4006 were used, the ICUR for AZE/FP compared with FP increased to $116,575 per QALY; when study MP4001 was excluded from the meta-analysis, the ICUR further increased to $131,291 per QALY. AZE is not marketed in Canada and therefore any assumption on its price relative to other nasal antihistamines

is highly uncertain. Further, AZE was dominated by FP in the base-case analysis. For these reasons, the results of AZE were not reported in the CDR reanalyses.

Conclusions

Several limitations were noted with the manufacturer's submission including source for efficacy data, analysis time horizon, impact of adverse events on quality of life, and adjustment of QALH based on age and gender. 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 FP was $194,592 per QALY. A price reduction analysis using CDR's most likely scenario showed that a price reduction of 55% would reduce the ICUR of AZE/FP compared with FP to $51,072 per QALY.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis using a trial-based model that estimated, on the basis of daily symptom scores (i.e., nasal and ocular symptoms), the differences between azelastine hydrochloride/fluticasone propionate (AZE/FP), FP, AZE, and placebo in terms of mean costs and effectiveness. The effectiveness is expressed as quality-adjusted life-hours (QALHs) that are subsequently converted to incremental quality-adjusted life-years (QALYs). Although the daily symptom scores were derived from study MP4001, the study did not capture health-related quality of life weights or resource use data;[3] therefore, predicted EuroQol 5-Dimensions Questionnaire (EQ-5D) scores on each day of the trial, for each comparator, were estimated based on patients' symptom scores. The predicted EQ-5D scores were calculated by applying a mapping algorithm on symptoms based on analyses of UK survey data that captured observational data on symptoms and EQ-5D. The model's time horizon was set at 14 days, consistent with the 14-day treatment period in study MP4001, and from the perspective of the Ministry of Health.

2. MANUFACTURER'S BASE CASE

Over the 14-day time horizon, total costs were $10.25, $[redacted], and $[redacted] for FP, AZE, and AZE/FP, respectively; total QALHs were 242.530, [redacted], and [redacted] for FP, AZE, and AZE/FP, respectively.

The manufacturer's sequential analysis showed that FP resulted in an incremental cost-utility ratio (ICUR) of $12,223 per QALY, AZE was dominated by FP, and AZE/FP resulted in an ICUR of $70,957 per QALY compared with FP ($31,936 per QALY compared with placebo). Detailed results are presented in Table 11 and Table 12 in Appendix IV.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

Uncertainty in the analyses was tested by the manufacturer through conducting a series of one-way deterministic sensitivity analyses and probabilistic sensitivity analyses based on bootstrapping of the trial data on daily symptoms (i.e., EQ-5D). The results of the one-way sensitivity analyses show that removing a quality of life adjustment to account for differences in age and gender between study MP4001 treatment arms had the most significant impact on the ICUR for AZE/FP versus FP. The probabilistic sensitivity analysis showed that AZE/FP had the highest likelihood of cost-effectiveness at a willingness-to-pay threshold above $73,000 per QALY, while FP had the highest probability of cost-effectiveness at thresholds ranging between $12,000 and $73,000 per QALY. At a threshold of $50,000 per QALY, AZE had a 10% chance of being cost-effective, the highest probability for this treatment.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Data source for comparative effectiveness:** The CADTH Common Drug Review (CDR) identified several limitations with the data sources used to derive the efficacy estimates for AZE/FP compared with AZE, FP, and placebo in the economic analysis:
  - The manufacturer's base-case analysis was based on study MP4001 only, although it was not considered a pivotal study by Health Canada as it used commercial formulations of AZE and FP as active comparator groups.[4,5] Further, as noted in the CDR Clinical Review Report, the treatment effect of AZE/FP was relatively greater in study MP4001, in which different vehicles were used, than in the three pivotal studies in which identical vehicle was used for all drugs.
  - The manufacturer-submitted economic model included a scenario analysis using pooled efficacy data from all studies (MP4001, MP4002, MP4004, and MP4006); however, no description of the analysis or its results was provided in the pharmacoeconomic (PE) report for this submission. Results of the scenario analysis showed AZE/FP, compared with placebo and FP, resulting in ICURs of $38,301 per QALY and $116,575 per QALY, respectively.
  - Although CDR reviewers considered the 14-day trials (MP4001, MP4002, MP4004, and MP4006) similar in terms of study design, study duration, and patient demographics (see CDR Clinical Review Report for details), the Health Canada Reviewer's Report indicated that the results of a meta-analysis submitted by the manufacturer based on all four studies were skewed by the results of study MP4001, which tended to have more favourable treatment differences over monotherapy.[5] As study MP4001 was not considered a pivotal study by Health Canada and the FDA, the manufacturer should have assessed the impact of using the efficacy data from the meta-analysis of the three pivotal clinical trials (MP4002, MP4004, and MP4006).
- **Duration of treatment per seasonal allergic rhinitis episode:** The manufacturer limited the time horizon to 14 days based on the 14-day treatment duration defined in study MP4001 and results of an online UK-based survey that indicated the mean episode duration was 12.5 days. Based on clinical input from the CDR expert for this review, patients with severe seasonal allergic rhinitis (SAR) will require between two and four weeks of treatment (14 to 28 days), depending on type and peak pollen exposure. Expert opinion also indicated that two weeks of treatment is appropriate to determine efficacy, but wouldn't reflect typical use.
- **Adjustment of quality of life for age and gender:** The manufacturer's PE report notes that the baseline demographics of study MP4001 varied between groups and therefore required adjustment based on gender and age. The manufacturer justified the adjustment based on the differences' potential impact on the incremental QALHs and ultimately the incremental costs between treatment arms. In study MP4001, mean age varied between 38.1 and 39.9 years old, and the proportion of females varied between 64% and 68% between treatment groups. The clinical study report for MP4001[6] does not report any *P* value, but states that all four of the treatment groups were comparable with regard to demographic and baseline clinical characteristics. It is therefore unclear why such an adjustment was made. Additional information was provided by the manufacturer to elaborate further on how the adjustment was performed. However, as reported in the Appendix A of the manufacturer's PE report, results of multiple regression models — with EQ-5D as dependent variable and nasal and ocular symptom scores, age, and gender as independent covariates — had consistently shown that the covariate of female gender never reached statistical significance, while age was significant across all models. It is therefore hard to justify why gender would be factored into the manufacturer's adjustment for demographic differences and final mapping algorithm to estimate EQ-5D scores.

- **Impact of adverse events on quality of life:** The manufacturer's base-case analysis did not include the impact of adverse events on patient quality of life, but instead conducted sensitivity analyses examining the potential impact. However, CDR identified limitations with the methodology applied by the manufacturer to incorporate the impact of adverse events that put into question the validity of the results of the sensitivity analysis on adverse events. Although evidence from study MP4001 showed AZE/FP to have the highest rates of dysgeusia compared with other treatments, there are insufficient data on the effects of dysgeusia on quality of life. The CDR clinical expert for this review confirmed dysgeusia's impact on compliance, especially with adolescent patients.
- **Direct costs excluded from analysis:** For the base-case analysis, the manufacturer included the medication costs for 14 days of treatment, assuming full compliance. However, based on the health care payer perspective of the analysis, other direct costs, such as co-medications and physician visits, should have been included. The resource use associated with co-medications and physician visits was included in a sensitivity analysis and was based on an international patient survey as the relevant studies for AZE/FP did not collect resource use or quality of life data.[7] Based on published Canadian qualitative studies and input from Canadian specialists, the manufacturer assumed such costs (co-medications and physician visits) to have minimal impact, and therefore were only included in sensitivity analyses.[8,9]
- **Mapping of utility scores:** Study MP4001 did not record utility measures and relied on symptomatic diary entries as its main clinical data. To derive the utility data required to calculate QALY gains, the manufacturer applied a mapping algorithm to symptom scores and demographics from study MP4001 to predict EQ-5D scores. Although the Guidelines for the Economic Evaluation of Health Technologies: Canada[10] indicates that the use of mapping in the absence of available utility values is appropriate, mapping increases the uncertainty and error regarding the utility estimates.
- **Lack of comparison with other nasal corticosteroids:** the manufacturer included only a comparison with single components. However, a literature search performed by CDR (see CDR Clinical Review Report, Appendix 7) indicated that limited evidence from two systematic reviews[11,12] suggests equivalent efficacy and safety of intranasal corticosteroids. Therefore, considering that there are other cheaper nasal corticosteroids reimbursed by drug plans potentially clinically equivalent to FP, it would have been a more conservative approach for the manufacturer to use the lowest unit price (i.e., budesonide $0.3373 daily).

5. CADTH COMMON DRUG REVIEW ANALYSES

CDR conducted a number of reanalyses to examine the impact of the limitations identified with the manufacturer's economic evaluation. However, due to structural limitations with the submitted economic model, CDR was unable to conduct a sensitivity analysis varying the treatment duration beyond the manufacturer's default 14 days. Furthermore, CDR reviewers could not run sensitivity analyses on adverse events due to structural limitations with the model and limited evidence available on impact of AEs associated with treatment of SAR on quality of life; however, it is expected that inclusion of AEs will result in increased ICURs for AZE/FP compared with other treatments, because of the higher rates of adverse events in the AZE/FP treatment groups; e.g., the rate of dysgeusia in AZE/FP compared with FP was 3.5% and 0.5%, respectively, based on pooled data of studies (MP4002, MP4004, and MP4006) (see CDR Clinical Review Report). Finally, as resource use associated with co-medications and physician visits was based on a UK patient survey and input from advisors, due to a scarcity of Canadian published data, verification of model estimates on resource use for co-medications and physician visits was not possible.

Efficacy Data Sourced From Pooled Studies
Based on similarity among the four clinical trials in terms of design, duration, and patient demographics, CDR performed an analysis using the pooled studies (MP4001, MP4002, MP4004, and MP4006). The resulting ICURs for AZE/FP compared with placebo and FP were $38,301 per QALY and $116,575 per QALY, respectively (Table 14, in Appendix IV).

Further, as study MP4001 was not considered a pivotal study by Health Canada and the FDA, CDR performed an additional analysis in which study MP4001 was excluded from the meta-analysis; i.e., using only pooled results from MP4002, MP4004, and MP4006. The resulting ICURs for AZE/FP compared with placebo and FP were $38,583 per QALY and $131,291 per QALY, respectively (Table 15, in Appendix IV).

Exclusion of Quality-Adjusted Life-Hours Adjustment
Due to structural limitations with the manufacturer-submitted economic model, CDR was unable to assess the impact of adjusting the QALHs based solely on age (both age and gender had to be considered simultaneously). Therefore, CDR conducted a reanalysis that excluded the QALH adjustments based on both age and gender that were not appropriately justified by the manufacturer or were not deemed to be clinically relevant by the clinical expert for this review. The resulting ICURs for AZE/FP compared with placebo and FP were $31,141 per QALY and $122,405 per QALY, respectively (Table 16, in Appendix IV).

CADTH Common Drug Review Revised Base Case
A multi-way sensitivity analysis by CDR combined the exclusion of the QALH adjustments based on age and gender, as well as the use of efficacy data from the pooled studies of AZE (MP4001, MP4002, MP4004, and MP4006). The resulting ICURs for AZE/FP compared with placebo and FP were $40,861 per QALY and $194,592 per QALY, respectively (Table 17, in Appendix IV).

Direct Treatment Costs
The direct treatment costs used by the manufacturer were based on a price list that is not publicly available; verification of the cost per doses for the comparators included was therefore not possible. Moreover, there is uncertainty regarding the estimated cost per dose and subsequently the cost per 14-day episode attributed to levocabastine, the only intranasal antihistamine available in Canada, as the manufacturer did not provide a transparent source for the listing cost of levocabastine nasal spray in Canada used in the analysis.

Price Reduction Scenario
A price reduction analysis was conducted on both the manufacturer's base-case analysis and the CDR's most likely scenario analysis. The results showed that using the manufacturer's base-case analysis, a price reduction of approximately 25% would result in an ICUR of AZE/FP compared with FP of $47,169 per QALY (Table 2). Using CDR's most likely scenario based on pooled study population and excluding any adjustments based on gender and age, a price reduction of greater than 55% would lead to an ICUR of $51,072 per QALY.

TABLE 2: CADTH COMMON DRUG REVIEW REANALYSIS PRICE REDUCTION SCENARIOS

ICURs of AZE/FP Versus FP ($/QALY)		
Price	**Base-case analysis submitted by manufacturer**	**CDR's most likely scenario**
Submitted	$70,957	$194,592
10% reduction	$61,442	$168,497
25% reduction	$47,169	$129,355
50% reduction	$23,381	$64,119
55% reduction	$18,623	$51,072
60% reduction	$13,865	$38,024
75% reduction	AZE/FP dominant	AZE/FP dominant

AZE = azelastine; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; CDR = CADTH Common Drug Review; FP = fluticasone propionate; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

6. ISSUES FOR CONSIDERATION

Utilization of intranasal corticosteroids in Canada: With evidence suggesting similar efficacy and safety among intranasal corticosteroids (see CDR Clinical Review Report, Appendix 6), and the availability of less costly intranasal corticosteroids than FP, a utilization analysis was done to illustrate the market shares of intranasal corticosteroids in Canada using PharmaStat data from IMS Health Canada Inc., 2014.[13] The results showed that FP ranks fifth in market shares in Canada with 7.35% of claims in 2014, behind ciclesonide (34.94%), mometasone (33.70%), budesonide (11.66%), and fluticasone furoate (8.91%).[13] An exploratory analysis was conducted using CDR's most likely scenario and lowest publicly available unit cost for an intranasal corticosteroid in Canada, budesonide 128 mcg ($10.12 per bottle, $0.0843 per spray), based on evidence suggesting equivalent efficacy and safety of intranasal corticosteroids.[11,12] The resulting ICUR for AZE/FP compared with budesonide was $230,381 per QALY, compared with $194,592 for AZE/FP versus FP.

7. PATIENT INPUT

Input from one patient group indicated that availability of a new treatment with the potential for more rapid treatment onset and greater symptom reduction was reported as important by patients. None of the patients surveyed had any experience with AZE/FP. Patients reported currently using prescription oral antihistamines, intranasal corticosteroids, antihistamine drops, and over-the-counter products (e.g., oral antihistamines). Patients were interested in a treatment that could provide specific benefits such as improved nasal breathing and sleep in addition to reduction in nasal congestion; throat irritation; persistent coughing; itchy eyes, nose, and throat; watery eyes; loss of sense of taste and smell; and fatigue.

8. CONCLUSIONS

Several limitations were noted with the manufacturer's submission, including source for efficacy data, analysis time horizon, impact of adverse events on quality of life, and adjustment of QALH based on age and gender. 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 FP was $194,592 per QALY. A price reduction analysis using the CDR's most likely scenario showed that a price reduction of 55% would reduce the ICUR of AZE/FP compared with FP to $51,072 per QALY.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 3 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and, as such, may not represent the actual costs to public drug plans.

TABLE 3: COST COMPARISON TABLE FOR DYMISTA FOR THE TREATMENT OF SEASONAL ALLERGIC RHINITIS

Drug/ Comparator	Strength	Dosage Form	Unit Cost ($)[a]	Usual Dose	Cost per Dose ($)[b]	Average Daily Cost ($)
Azelastine HCl and fluticasone propionate (Dymista)	137 mcg/ 50 mcg /spray (120 doses)	Suspension (metered-dose spray)	[redacted][c]	1 spray/nostril twice daily	[redacted]	[redacted]
Nasal Antihistamines						
Levocabastine (Livostin)	50 mcg/spray (0.5 mg/mL; 15 mL, 150 doses)[d]	Nasal spray	1.9667[e]	2 sprays/nostril twice daily Max: 8 sprays/nostril per day	0.1967	1.5734 to 3.1467
Nasal Corticosteroids						
Beclomethasone dipropionate (generic)	50 mcg/spray (200 doses)	Aqueous suspension nasal spray	12.2600	2 sprays/nostril twice daily Max: 12 sprays per day	0.0613	0.4904 to 0.7356
Fluticasone propionate (generics)	50 mcg/spray (120 doses)	Aqueous nasal spray	21.9700[f]	2 sprays/nostril once daily or 1 spray/nostril twice daily Max: 4 sprays/nostril per day	0.1831	0.7323 to 1.4647
Fluticasone furoate (Avamys)	27.5 mcg/ spray (120 doses)	Suspension (metered-dose spray)	20.7300[g]	2 sprays/nostril once daily Maintenance: May reduce to 1 spray/nostril once daily Max: 2 sprays in each nostril per day	0.1728	0.3456 to 0.6912
Mometasone furoate (Nasonex)	50 mcg/spray (140 doses)	Aqueous nasal spray	29.6700[f]	2 sprays/nostril once daily May reduce dose to 1 spray	0.2119	0.4239 to 1.6954

Drug/ Comparator	Strength	Dosage Form	Unit Cost ($)[a]	Usual Dose	Cost per Dose ($)[b]	Average Daily Cost ($)
Mometasone furoate (generic)			23.4220[h]	in each nostril Max: 4 sprays in each nostril per day	0.1673	0.3346 to 1.3384
Budesonide (generic)	100 mcg/ spray (165 doses)	Metered-dose nasal spray	12.7400	2 sprays/nostril once daily or 1 spray/nostril twice daily	0.0772	0.3088
Budesonide (Rhinocort Turbuhaler)	100 mcg/ dose (200 doses)	Metered-dose nasal aerosol	24.4600	2 sprays/nostril once daily	0.1208	0.4892
Budesonide (generic)	64 mcg/spray (120 doses)	Metered-dose nasal spray	10.1200[f]	2 sprays/nostril once daily or 1 spray/nostril twice daily	0.0843	0.3373
Budesonide (Rhinocort Aqua)			11.0400		0.0908	0.3680
Ciclesonide (Omnaris)	50 mcg/spray (120 doses)	Actuation metered-dose nasal spray	25.7800	2 sprays (50 mcg/spray) in each nostril once daily	0.2148	0.8593
Triamcinolone acetonide (Nasacort AQ)[i]	55 mcg/spray (120 doses)	Aqueous nasal spray	0.2000[j]	2 sprays/nostril once daily If possible, reduce to 1 spray in each nostril once daily	0.2000	0.8000
Flunisolide (generic)	25 mcg/spray (0.025%) (25 mL pack)	Solution (metered-dose pump)	18.8100	2 sprays/nostril twice daily Max: 6 sprays/nostril per day	0.9405	0.7524 to 1.1286
Other Nasal Sprays						
Sodium cromoglycate (Rhinaris-CS)	2% w/v (0.13 mL per dose; 13 mL to 26 mL bottles)	Nasal spray	0.5292[e]	1 spray/nostril six times daily Maintenance: 1 spray/nostril, 2 to 3 times daily	0.0690	0.2752 to 0.8256
Oral Antihistamines						
Cetirizine	20 mg	Tablet	0.8595[i]	½ tablet, once daily. Titrate up to 1 tablet daily if required	0.4298 to 0.8595	0.4298 to 0.8595

Drug/ Comparator	Strength	Dosage Form	Unit Cost ($)[a]	Usual Dose	Cost per Dose ($)[b]	Average Daily Cost ($)
Oral Leukotriene Receptor Antagonists						
Montelukast (generics)	10 mg	Tablet	0.8195[f]	One tablet, once daily	0.8195	0.8195

HCl = hydrochloride.

[a] Note: Unit cost is the cost specified by the public formularies; the unit may differ between provinces. See notes below for further clarification.
[b] Note: Cost per dose is a cost per metered spray, except when referring to the orals, where it is cost per tablet.
[c] Source: Manufacturer's submission.[8]
[d] Note: The number of sprays is an assumption based on information from the Australian Pharmaceutical Benefits Scheme formulary, which indicates 100 actuations for 10 mL Livostin.[14,15]
[e] Source: Nova Scotia drug Formulary (March 2015).[16] Unit price is per mL.
[f] Source: Saskatchewan Drug Formulary (March 2015).[17]
[g] Source: Quebec Drug Formulary (April 2015).[18]
[h] Source: British Columbia Drug Formulary (April 2015).[19]
[i] Available without prescription.
[j] Yukon drug formulary (March 2015).[20] Unit price is per dose (tablet or spray).
Source: Ontario online drug plan formulary February 26th, 2015 unless indicated otherwise (accessed March 2015)[21]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 4: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS AZE/FP RELATIVE TO PLACEBO?

AZE/FP Vs. Placebo	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$3.65 per QALH $31,936 per QALY					

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; CE = cost-effectiveness; NA = not applicable; QALH = quality-adjusted life-hour; QALY = quality-adjusted life-year.
Note: Based on manufacturer's results.

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS AZE/FP RELATIVE TO AZE?

AZE/FP Vs. AZE	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$4.40 per QALH $38,546 per QALY					

AZE = azelastine hydrochloride; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; CE = cost-effectiveness; NA = not applicable; QALH = quality-adjusted life-hour; QALY = quality-adjusted life-year; vs. = versus.
Note: Based on manufacturer's results.

TABLE 6: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS AZE/FP RELATIVE TO FP?

AZE/FP Vs. FP	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$8.10 per QALH $70,957 per QALY					

AZE = azelastine hydrochloride; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; CE = cost-effectiveness; NA = not applicable; QALH = quality-adjusted life-hour; QALY = quality-adjusted life-year; vs. = versus.
Note: Based on manufacturer's results.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 7: SUBMISSION QUALITY

	Yes/ Good	Somewhat/Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	None		
Was the material included (content) sufficient?		X	
Comments	None		
Was the submission well organized and was information easy to locate?		X	
Comments	None		

TABLE 8: AUTHOR INFORMATION

Authors	Affiliations
Donna Lawrence Laura Gibson Dylan Lamb-Palmer	PDCI Market Access Inc.

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis			X

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis using a trial-based model that estimates, on the basis of daily symptom scores, the differences between AZE/FP (a fixed-dose combination of azelastine hydrochloride and fluticasone propionate), FP, AZE, and placebo in terms of mean costs and effectiveness. The effectiveness was expressed as quality-adjusted life-hours (QALHs), which were subsequently converted to incremental quality-adjusted life-years (QALYs). The model's time horizon was set at 14 days, consistent with the 14-day treatment period in study MP4001, and from the perspective of the Ministry of Health.

Study MP4001 did not assess health-related quality of life weight or resource use data appropriate for use in the cost-effectiveness analysis; rather, these data were collected in an online survey of UK patients.[7] Symptom data, demographics, and EuroQol 5-Dimensions Questionnaire (EQ-5D) data were included as the basis for the development of a utility mapping algorithm to convert the total nasal symptom score (TNSS) and total ocular symptom score (TOSS) data collected in study MP4001 to EQ-5D, in order to calculate the incremental QALY for the cost-effectiveness analysis.[7] This mapping algorithm was then used to translate clinical data from trial MP4001 into EQ-5D utility measures. The patient survey also collected additional data on resource use and productivity costs in moderate-to-severe seasonal allergic rhinitis (SAR) patients.[7]

Multiple regression techniques have been applied with EQ-5D as dependent end point and nasal and ocular symptom scores, age, and gender as independent covariates. Basic analyses were conducted using ordinary least square models that have been amended by other models such as Tobit and censored least absolute deviations models to evaluate the impact of the estimation method. Across all models, age was always found to be a significant factor ($P \leq 0.05$), but female gender never reached statistical significance. Nasal congestion and watery eyes were the symptoms with coefficients that are consistently significant with the correct sign; i.e., increasing symptoms reduce the EQ-5D utility score. The coefficients of the remaining symptoms do not reach statistical significance. Analyses have been conducted for the full set of all 1,000 patients, as well as for subgroups. The final mapping algorithm was:

EQ-5D = 1.034 + 0.009 × female – 0.003 × age – 0.053 × nasal congestion – 0.055 × watery eyes
Female to be set to 1 for female and 0 for male
Age to be considered continuously
Symptom score to be considered from 0 = none to 3 = severe.
Source: Manufacturer Pharmacoeconomic Submission.[8]

After applying the algorithm to the data of study MP4001, the mean daily EQ-5D score under each treatment was computed, summed up over the 14-day treatment period, and multiplied by 24 to yield the number of QALHs over this period. Perfect health for 14 days was estimated to be equal to a QALH score of 336. The manufacturer noted that baseline demographics (age and gender) varied between treatment arms in study MP4001, and that difference in age and gender affected the incremental QALH and costs, thereby requiring the adjustment of QALHs based on age and gender.

TABLE 9: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Quantitative assessment of treatment benefits was based on study MP4001; a randomized, double-blind, direct head-to-head comparison of AZE/FP versus FP, AZE, and placebo over the length of 14 days.[3]	Similarity of study design, study duration, and patient demographics was detected among MP4001, MP4002, MP4004, and MP4006. Rationale for not using pooled study data was not provided.
Natural history	Baseline patient characteristics, demographic, and baseline TOSS/TNSS data were obtained from study MP4001.[3]	
Utilities	Study MP4001 did not assess health-related quality of life.[3] Data were collected via an online survey of UK patients.[7] The survey results were used to develop a mapping algorithm to estimate EQ-5D utility values from nasal and ocular symptom scores and demographics. Age and gender were included in the mapping algorithm. The resulting mapping algorithm was used to translate clinical data (TNSS/TOSS) from study MP4001 into EQ-5D utility scores.	Clinical expert opinion and evidence from the manufacturer did not support different treatment effects on quality of life based on gender in patients with SAR.
Resource use	Study MP4001 did not collect resource use data.[3]	In sensitivity analyses, the model was adapted to include costs applicable to the Canadian setting using a qualitative Canadian study[9] and input from Canadian treating specialists.
AEs	AEs were not included in the base-case analysis, as safety and tolerability of treatments were considered similar by the manufacturer based on results of study MP4001.[3] A sensitivity analysis explored the impact of AEs on costs and quality of life (utility) based on manufacturer assumptions and Canadian clinical advisors.	Method applied to incorporate impact of AEs on quality of life is not clear and appears to apply similar weights to all AEs.

Data Input	Description of Data Source	Comment
Mortality	Mortality was not included in the manufacturer's submitted model.	
Costs		
Drug	Unit costs for medications were obtained from the AQPP price list (2014).[8] Because azelastine is not available in Canada, the azelastine medication cost was calculated from the list cost of levocabastine nasal spray (Livostin).[8]	Oral antihistamines, with few exceptions, are typically not reimbursed by public drug plans in Canada. No public price list is available from AQPP. The manufacturer did not supply the source for the listing cost of levocabastine nasal spray.
Co-medications	Costs for co-medications were included only in a sensitivity analysis. Costs for co-medications were based on the resource use recorded by FP patients with moderate-to-severe SAR in the UK patient survey.[7] As no cost data for AZE and AZE/FP were available from the UK survey, the cost data were approximated by scaling the FP costs in proportion to the quality-adjusted life-hour advantage.	Verification of resource use estimates and generalizability to Canadian clinical practice was not possible in light of limited evidence.

AE = adverse event; AQPP = Association québécoise des pharmaciens propriétaires; AZE = azelastine hydrochloride; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; EQ-5D = EuroQol 5-Dimensions Questionnaire; FP = fluticasone propionate; SAR = seasonal allergic rhinitis; TNSS = total nasal symptom score; TOSS = total ocular symptom score.

TABLE 10: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Comparison of AZE/FP with FP, AZE, and placebo was based on the treatment comparison in study MP4001.	The monotherapy comparators used in MP4001, marketed AZE, and commercially available generic FP are formulated with different vehicles than AZE/FP (Dymista). Health Canada and the US FDA considered MP4001 as non-pivotal trial, a secondary support for efficacy and safety. Further, the treatment effect of AZE/FP was relatively greater in study MP4001, in which different vehicles were used, than in the 3 pivotal studies in which identical vehicle was used for all drugs.
The economic model assumes a linear relationship between quality of life improvements and health care cost reductions.	Likely appropriate, according to clinical expert opinion.
Because AZE is not available in Canada, the cost of levocabastine, the only intranasal antihistamine available in Canada, was used.	Likely appropriate. Based on limited evidence, there is no difference in the efficacy of intranasal antihistamines and AZE.
A time horizon of 14 days per symptom episode was used.	This time horizon was supported by an online UK patient survey that found the mean SAR episode to last 12.5 days; this may not be relevant to Canada, as the geographical distribution of pollens between countries will likely be different.
AEs did not affect quality of life or costs in the base-case analysis.	Possible bias in favour of AZE/FP as results from study MP4001 indicated higher incidence of dysgeusia in AZE/FP group. Method applied to incorporate AEs in sensitivity analysis is questionable as it applies similar disutility across all reported AEs on quality of life.
In a sensitivity analysis to explore the potential impact of AEs, a 0.05 utility decrement was applied for all AEs for the 14-day trial period, along with an assumed cost of treatment for all AEs of $10.	No source or justification was identified to justify the values used by the manufacturer for the sensitivity analysis.
It was assumed that at least 2 symptom episodes of 14 days would occur each year and that the costs of 14-day treatment were included.	According to clinical expert opinion, patients with severe SAR would require between 2 and 4 weeks of treatment.

AE = adverse event; AQPP = Association québécoise des pharmaciens propriétaires; AZE = azelastine hydrochloride; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; EQ-5D = EuroQol 5-Dimensions Questionnaire; FP = fluticasone propionate; SAR = seasonal allergic rhinitis.

Manufacturer's Results

Table 11 shows the manufacturer-reported disaggregated results of the reference case analysis, which showed FP to be the least costly treatment ($10.25) while AZE/FP was the most costly ($[redacted]).

TABLE 11: REFERENCE CASE — DISAGGREGATED RESULTS

	Placebo	AZE	FP	AZE/FP
Clinical Effectiveness				
QALHs (14 days)	235.18247	[redacted]	244.37279	[redacted]
Adjustment for age and gender	0.00	–0.29	–1.84	–0.28
Adjusted QALHs (14 days)	235.18	[redacted]	242.53	[redacted]
QALY index relative to FP	1.08	1.01	1.00	0.96
Total QALHs	**235.18**	[redacted]	**242.53**	[redacted]
Costs				
Principal treatment	$0.00	$[redacted]	$10.25	$[redacted]
Total costs	**$0.00**	**$[redacted]**	**$10.25**	**$[redacted]**

AZE = azelastine; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; FP = fluticasone propionate; QALH = quality-adjusted life-hour; QALY = quality-adjusted life-year.
Source: Manufacturer Pharmacoeconomic submission (Table 14, page 39).[8]

The manufacturer presented a sequential analysis in which the incremental cost-utility ratio (ICUR) of each treatment is determined against the next less costly non-dominated therapy (Table 12). Compared with placebo, FP resulted in a cost per QALH of $1.40 and a cost per QALY of $12,223. AZE was dominated by FP as it produced fewer benefits (QALH) at greater costs compared with FP. AZE/FP, when compared with FP individually, resulted in a cost per QALH of $8.10 and a cost per QALY of $70,957.

TABLE 12: REFERENCE CASE — COST-EFFECTIVENESS RESULTS

Treatment	Total Cost	Total QALHs	Incremental Costs (vs. Placebo)	Incremental QALHs (vs. Placebo)	ICUR (vs. Placebo) ($/QALY	Sequential ICUR ($/QALY)
Placebo		235.182	-	-		-
FP	$10.25	242.530	$10.25	7.348	$12,233	$12,223
AZE	$[redacted]	[redacted]	$[redacted]	[redacted]	$27,207	Dominated
AZE/FP	$[redacted]	[redacted]	$[redacted]	[redacted]	$31,936	$70,957

AZE = azelastine; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; FP = fluticasone propionate; ICUR = incremental cost-utility ratio; QALH = quality-adjusted life-hour; QALY = quality-adjusted life-year; vs. = versus.
Source: Adapted from the Manufacturer Pharmacoeconomic submission (Table 15, page 40).[8]

Summary of Manufacturer's Sensitivity Analyses

Uncertainty in the analyses was tested by the manufacturer through a series of one-way deterministic sensitivity analyses and probabilistic sensitivity analyses based on bootstrapping of the trial data on daily symptoms (i.e., EQ-5D). Because resource use was assumed by the manufacturer to be equal across treatment groups, it was not included in the probabilistic sensitivity analysis.

Deterministic Sensitivity Analyses

The parameters and assumptions varied by the manufacturer are listed in Table 13. The results of the one-way sensitivity analyses show that removing a quality of life adjustment to account for differences

in age and gender between study MP4001 treatment arms had the most significant impact on the ICUR for AZE/FP versus FP.

TABLE 13: DETERMINISTIC SENSITIVITY ANALYSES

Sensitivity Analysis	Reference Case Input Value	Alternative Input Values	Rationale	ICUR for AZE/FP vs.:		
				Placebo	AZE	FP
Base case				$31,936	$38,546	$70,957
Impact of QoL on costs	100%	75%, 50%, 25%, 0%	To test the effect of utility (QALY index)	$31,936	$38,546	$70,957
Impact of symptoms on QALH	100% symptom utility mapping algorithm	95% 90% 85% 80%	To test the impact of symptom regression coefficients on the QALH	$33,616 $35,484 $37,751 $39,920	$40,575 $42,829 $45,348 $48,183	$74,691 $78,841 $83,478 $88,696
Symptoms for utilities	Individual symptom scores	TNSS/TOSS	To test the effect of the chosen mapping algorithm	$30,358	$52,036	$68,149
AEs (QoL)	AE impact not included	AE impact on QoL included (5%)	To test the effect of a utility decrement due to total AEs	$34,244	$49,494	$89,892
AEs (costs)	AE impact not included	AE impact on costs included ($10)	To test the effect of costs due to total AEs	$32,287	$39,699	$72,055
Adverse events (cost + QoL)	AE impact not included	AE impact on costs and QoL included	To test the effect of a utility decrement and costs due to total AEs	$34,621	$50,975	$91,284
QALH adjustment	Yes	No	To test the effect of the age and gender QALH adjustment	$31,141	$38,622	$122,405
Resource use costs	No	Yes	To test the effect of including resource use costs in the model	$29,986	$36,596	$69,007

AE = adverse event; AZE = azelastine; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; FP = fluticasone propionate; ICUR = incremental cost-utility ratio; QALH = quality-adjusted life-hour; QALY = quality-adjusted life-year; QoL = quality of life; TNSS = total nasal symptom score; TOSS = total ocular symptom score; vs. = versus.
Source: Adapted from the Manufacturer Pharmacoeconomic submission (Table 17, page 42).[8]

Probabilistic Sensitivity Analysis

The manufacturer conducted probabilistic sensitivity analyses based on bootstrapping of the trial data on daily symptoms which, in turn, varied the resulting EQ-5D scores over 1,000 iterations. Resource use was assumed by the manufacturer to be equal across treatment arms. The cost-effectiveness acceptability curves indicated that AZE/FP had the highest likelihood of cost-effectiveness versus the comparators (i.e., AZE, FP, and placebo) at a willingness-to-pay threshold above $73,000 per QALY. At a willingness-to-pay threshold of $70,000 per QALY, AZE/FP had an approximately 50% and higher probability of being cost-effective when compared with FP alone. Meanwhile, FP had the highest probability of being cost-effective over thresholds ranging between $12,000 and $73,000 per QALY (88%

chance at $29,000 per QALY). At a threshold of $50,000 per QALY, AZE had a 10% chance of being cost-effective, the highest probability for this treatment.

CADTH Common Drug Review Reanalysis

The CADTH Common Drug Review (CDR) attempted to conduct a number of reanalyses to examine the impact of the limitations identified with the manufacturer's economic evaluation. However, due to structural limitations with the submitted economic model, CDR was unable to conduct a sensitivity analysis in the following scenarios:

1. Varying the treatment duration beyond the manufacturer's default 14 days, although it is expected that the costs associated with treatment duration will be higher in patients with more severe SAR.
2. Structural limitations with the model and available evidence on SAR were factors that prevented CDR from being able to conduct sensitivity analyses on adverse events; however, it is expected that inclusion of adverse events will result in increased ICURs for AZE/FP compared with other treatments.
3. Structural limitations with the model did not allow CDR to assess the impact of adjusting the QALHs on age in separation from gender, because age was considered a significant covariate, as opposed to gender, which was not significant in any of the regression models.
4. Resource use associated with co-medications and physician visits was estimated on the basis of a UK patient survey and input from advisors due to scarcity of published Canadian data; therefore, verification of model estimates on resource use for co-medications and physician visits was not possible.

To address the remaining limitations identified in the submission, CDR conducted the following reanalyses using the manufacturer-submitted economic model. An analysis using the pooled study population from studies (MP4001, MP4002, MP4004, and MP4006) was conducted based on similarity among the four clinical trials in terms of design, duration, and patient demographics. Although the manufacturer's economic model included a scenario analysis using the pooled efficacy data from the studies on AZE/FP versus placebo, AZE, and FP, the manufacturer's pharmacoeconomic report did not provide a description of the methodology used for the pooled analysis, nor were results presented in the report (Table 14).

TABLE 14: RESULTS OF CADTH COMMON DRUG REVIEW ANALYSIS USING POOLED STUDY POPULATIONS (MP4001, MP4002, MP4004, AND MP4006)

Interventions	Total Costs	Total QALHs	Incremental Costs (vs. Placebo)	Incremental QALHs (vs. placebo)	ICUR (vs. placebo) ($/QALY)	Sequential ICUR ($/QALY)
Placebo	0.00	240.882	-	-	-	---
FP	$10.25	247.845	$10.25	6.962	$12,900	$12,900
AZE	$[redacted]	[redacted]	$[redacted]	[redacted]	$35,093	Dominated
AZE/FP	$[redacted]	[redacted]	$[redacted]	[redacted]	$38,301	$116,575

AZE = azelastine; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; FP = fluticasone propionate; ICUR = incremental cost-utility ratio; PL = placebo; QALH = quality-adjusted life-hour; QALY = quality-adjusted life-year.

Further, as study MP4001 was not considered a pivotal study by Health Canada and the US FDA, CDR performed an additional analysis where study MP4001 was excluded from the meta-analysis; i.e., using only pooled results from MP4002, MP4004, and MP4006 (Table 15).

TABLE 15: RESULTS OF CADTH COMMON DRUG REVIEW ANALYSIS USING POOLED STUDY POPULATIONS (MP4002, MP4004, AND MP4006)

Interventions	Total Costs	Total QALHs	Incremental Costs (vs. Placebo)	Incremental QALHs (vs. Placebo)	ICUR (vs. Placebo) ($/QALY)	Sequential ICUR ($/QALY)
Placebo	$0.00	241.239	-	-	-	-
FP	$10.25	248.387	$10.25	7.148	$12,564	$12,564
AZE	$[redacted]	[redacted]	$[redacted]	[redacted]	$35,145	Dominated
AZE/FP	$[redacted]	[redacted]	$[redacted]	[redacted]	$38,583	$131,291

AZE = azelastine; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; FP = fluticasone propionate; ICUR = incremental cost-utility ratio; PL = placebo; QALH = quality-adjusted life-hour; QALY = quality-adjusted life-year.

A reanalysis that excluded the QALH adjustments based on age and gender: This adjustment was not appropriately justified by the manufacturer. Based on expert opinion, gender is not likely to affect the efficacy of these treatments for this indication, thus confirming the results of the manufacturer's multiple regression techniques that showed lack of statistical significance for gender as an independent covariate. Age was recognized as a factor in patient compliance, especially among adolescent patients. However, structural limitations with the submitted model prevented the adjustment of QALH solely on age. According to the CDR clinical review, the proportion of adolescent patients in MP4001 did not exceed 10% of the study population (Table 16).

TABLE 16: RESULTS OF CADTH COMMON DRUG REVIEW ANALYSIS EXCLUDING QALH ADJUSTMENTS TO AGE AND GENDER

Interventions	Total Costs	Total QALHs	Incremental Costs (vs. Placebo)	Incremental QALHs (vs. Placebo)	ICUR (vs. Placebo) ($/QALY)	Sequential ICUR ($/QALY)
Placebo	0.00	235.182	-	-	-	---
FP	$10.25	244.373	$10.25	9.190	$9,773	$9,773
AZE	$[redacted]	[redacted]	$[redacted]	[redacted]	$26,031	dominated
AZE/FP	$[redacted]	[redacted]	$[redacted]	[redacted]	$31,141	$122,405

AZE = azelastine; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; FP = fluticasone propionate; ICUR = incremental cost-utility ratio; PL = placebo; QALH = quality-adjusted life-hour; QALY = quality-adjusted life-year.

CADTH Common Drug Review Multi-way Analysis

The pooled study population from studies (MP4001, MP4002, MP4004, and MP4006) as submitted by the manufacturer was consequently used in a multi-way sensitivity analysis by CDR that also excluded the QALH adjustments based on age and gender (Table 17).

TABLE 17: RESULTS OF CADTH COMMON DRUG REVIEW MULTI-WAY SENSITIVITY ANALYSIS

Interventions	Total Costs	Total QALHs	Incremental Costs (vs. Placebo)	Incremental QALHs (vs. Placebo)	ICUR (vs. Placebo) ($/QALY)	Sequential ICUR ($/QALY)
Placebo	0.00	240.882	-	-	-	---
FP	$10.25	248.173	$10.25	7.290	$12,319	$12,319
AZE	$[redacted]	[redacted]	$[redacted]	[redacted]	$40,291	Dominated
AZE/FP	$[redacted]	[redacted]	$[redacted]	[redacted]	$40,861	$194,592

AZE = azelastine; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; FP = fluticasone propionate; ICUR = incremental cost-utility ratio; PL = placebo; QALH = quality-adjusted life-hour; QALY = quality-adjusted life-year.

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