CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

FLUTICASONE FUROATE/VILANTEROL (Breo Ellipta — GlaxoSmithKline Inc.) Indication: Asthma

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that fluticasone furoate/vilanterol (FF/VI) be listed for the once-daily maintenance treatment of asthma in patients aged 18 years and older with reversible obstructive airways disease, if the following conditions are met:

Conditions:
- List in a manner similar to other fixed-dose combination (FDC) inhaled corticosteroid (ICS)/long-acting beta-agonist (LABA) inhalers indicated for the treatment of asthma.
- Drug plan cost for FF/VI should not exceed the drug plan cost for the least expensive ICS/LABA inhaler.

Reasons for the Recommendation:
1. FF/VI was statistically significantly superior to ICS monotherapy in reducing exacerbations among patients at higher risk for exacerbations, and for improving lung function; however, data on important outcomes, such as quality of life, were limited. In addition, the efficacy of this product compared with other similar combination products remains uncertain.
2. At the submitted daily price ([redacted]), FF/VI 100/25 mcg is less costly than other medium-dose ICS/LABA combination therapies ($2.80 to $3.25 per day) and FF/VI 200/25 mcg is less costly than other high-dose ICS/LABA combination therapies ($3.62 to $5.59 per day).

Of Note:
- Due to the absence of a low-dose formulation, there is less flexibility with the dosing of FF/VI compared with other ICS/LABA inhalers for the treatment of asthma.

Background:
FF/VI is a once-daily FDC of the ICS fluticasone furoate and the LABA vilanterol, administered by the Ellipta inhaler. This product has a Health Canada indication for once-daily maintenance treatment of asthma in patients aged 18 years and older with reversible obstructive airways

disease. FF/VI is available as 100 mcg/25 mcg and 200 mcg/25 mcg dosage formats for the treatment of asthma.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of randomized controlled trials and pivotal studies of FF/VI in the treatment of asthma, a critique of the manufacturer's pharmacoeconomic evaluation, and information submitted by patient groups about outcomes and issues that are important to individuals living with asthma.

Patient Input Information
Two patient groups (i.e., the Ontario Lung Association and the British Columbia Lung Association) responded to the CDR call for patient input. Information was obtained from online surveys of asthma patients, from a certified respiratory educator, knowledge garnered through research and best practice guidelines, and experience from direct involvement with patients. The following is a summary of key information provided by the patient groups:

- Asthma can negatively affect many aspects of patients' lives. Common symptoms and challenges include shortness of breath, chronic coughs and wheezing, impact on physical and day-to-day activities, fatigue, difficulty fighting infections, difficulty managing weight loss, and impact on family life.
- The unmet needs with existing therapy identified by patients include medications that can improve lung function, halt disease progression, prevent or reduce hospitalization, improve quality of life, reduce asthma symptoms (e.g., shortness of breath, coughing, and fatigue), improve energy levels and appetite, and increase ability to fight infections.

Clinical Trials
The CDR systematic review included seven active-controlled, double-blind trials: HZA-714 (N = 313; 12 weeks), HZA-863 (N = 1,039; 12 weeks), HZA-827 (N = 610; 12 weeks), HZA-091 (N = 806; 24 weeks), HZA-829 (N = 587; 24 weeks), HZA-837 (N = 2,020; 24 to 76 weeks), and HZA-839 (N = 503; 52 weeks). The included studies compared the efficacy of FF/VI 100/25 mcg and/or 200/25 mcg to equivalent moderate- or high-dose ICS monotherapies (i.e., FF, fluticasone propionate [FP]), ICS/LABA combination therapy (i.e., FP/salmeterol [S]) and/or placebo. The included studies enrolled patients diagnosed with asthma, aged 12 years or older, with forced expiratory volume in one second (FEV_1) reversibility of ≥ 12% and ≥ 200 mL following short-acting beta-agonist (albuterol) inhalation. In nearly all of the studies, more than 60% of the study population was already using an ICS/LABA combination inhaler at the time of enrolment.

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

- Severe asthma exacerbation — defined according to the American Thoracic Society/European Respiratory Society taskforce guidelines.
- FEV_1 — defined as the volume of air that can be forcibly expired in one second after a full inspiration.
- Peak expiratory flow (PEF) — defined as the maximum flow achieved during an expiration delivered with maximal force starting from the level of maximal lung inflation.

- Asthma Quality of Life Questionnaire for 12 years and older (AQLQ +12) — a patient-reported, disease-specific health-related quality of life measure. AQLQ +12 includes 32 questions grouped into four domains: symptoms, activity limitations, emotional function, and environmental stimuli.
- Asthma Control Test (ACT) — a five-item patient-reported questionnaire on asthma control. Items capture the impact of asthma on work, school, or home activities; shortness of breath; nocturnal awakening; the use of rescue medication; and overall control.
- Asthma rescue-free days.
- Resource utilization.

Among the five lung-function studies, the weighted mean serial FEV_1 was the primary end point in HZA-863 and HZA-091 and the co-primary end point in HZA-829 and HZA-827. Change from baseline in evening PEF was the primary end point in HZA-714. In studies HZA-827 and HZA-829, change from baseline in trough evening FEV_1 was also a co-primary end point. The primary end point in HZA-837 was time to first severe asthma exacerbation. The co-primary end points in the safety study, HZA-839, were the number of participants with any adverse events or serious adverse events and the number of severe asthma exacerbations.

Efficacy

- In study HZA-837, the rate of severe asthma exacerbations per patient per year was 0.14 in FF/VI 100/25 mcg and 0.19 in FF 100 mcg. The hazard ratio for time to first severe asthma exacerbation was reported as follows:
  - FF/V 100/25 mcg versus FF 100 mcg: 0.795 (95% confidence interval [CI], 0.642 to 0.985; $P = 0.036$).
- In most studies, the differences in change in quality of life between treatments could not be compared statistically, as hierarchical testing was stopped before this outcome. Among those in which statistical testing was appropriate, changes in AQLQ +12 scores between FF/VI and other active treatments were not statistically significant. Mean differences in change from baseline in AQLQ +12 were reported as follows:
  - FF/VI 100/25 mcg versus FF 100 mcg: 0.08 ($P = 0.303$) in HZA-863
  - FF/VI 200/25 mcg versus FF 200 mcg: 0.05 ($P = 0.587$) in HZA-829.
- FF/VI 100/25 mcg led to a statistically significant greater improvement in least-squares mean change in ACT compared with FF 100 mcg in study HZA-863. In all other studies, statistical significance testing was stopped before this outcome.
  - FF/VI 100/25 mcg versus FF 100 mcg: 0.9 ($P = 0.002$) in HZA-863.
- There was inconsistency in the results between FF/VI 100/25 mcg and FF 100 mcg with regard to the outcome of FEV_1. There was no statistically significant difference in FEV_1 between FF/VI 100/25 mcg and FP/S 250/50 mcg while FF/V 200/25 mcg was associated with a statistically significant improvement in FEV_1 compared with FF 200 mcg and FP 500 mcg. Mean differences between groups were reported as follows:
  - FF/VI 100/25 mcg versus FF 100 mcg: 0.036 L ($P = 0.405$) in HZA-827, 0.077 L ($P = 0.014$) in HZA-863, and 0.089 L ($P < 0.001$) in HZA-837
  - FF/VI 200/25 mcg versus FF 200 mcg: 0.193 L ($P < 0.001$) in HZA-829
  - FF/VI 200/25 mcg versus FP 500 mcg: 0.210 L ($P < 0.001$) in HZA-829
  - FF/VI 100/25 mcg versus FP/S 250/25 mcg: −0.019 L (95% CI, −0.073 to 0.034) in HZA-091.
- Although several studies reported changes in evening PEF, statistical significance testing was possible only in HZA-863 and HZA-714, as testing was halted in the other trials due to

failure at a prior stage of the hierarchical tests. Mean differences between groups were reported as follows:
  - FF/VI 100/25 mcg versus FF 100 mcg: 24.2 L/min ($P < 0.001$) in HZA-863 and 12.3 L/min (95% CI, 5.8 to 18.8) in HZA-827
  - FF/VI 200/25 mcg versus FF 200 mcg: 30.7 L/min (95% CI, 22.5 to 38.9) in HZA-829
  - FF/VI 200/25 mcg versus FP 500 mcg: 28.5 L/min ($P < 0.001$) in HZA-714 and 26.2 L/min (95% CI, 18.0 to 34.3) in HZA-829.
- All treatment groups in the included studies showed an increase in the percentage of rescue-free days relative to baseline. FF/VI 100/25 mcg and 200/25 mcg were associated with a greater percentage of rescue-free days than the equivalent dose of FF:
  - FF/VI 100/25 mcg versus FF 100 mcg: 12.2 ($P < 0.001$) in HZA-863 and 10.6 (95% CI, 4.3 to 16.8) in HZA-827
  - FF/VI 200/25 mcg versus FF 200 mcg: 11.7 ($P < 0.001$) in HZA-829
  - FF/VI 200/25 mcg versus FP 500 mcg: 1.0 (95% CI, −7.3 to 9.2) in HZA-714 and 6.3 (95% CI, −0.4 to 13.1) in HZA-829.
- Reports on unscheduled health care resource use were low across all treatment arms and studies.

Harms (Safety and Tolerability)

- The most frequently reported adverse events were upper respiratory tract infections (0% to 18%), headaches (< 1% to 23%), and nasopharyngitis (4% to 20%). Similar rates of adverse events were reported with FF/VI compared with the other active treatments. The proportions of patients who experienced at least one adverse event were:
  - HZA-827: FF/VI 100/25 mcg, 29%; FF 100 mcg, 25%; and placebo, 21%
  - HZA-863: FF/VI 200/25 mcg, 36%; FF/VI 100/25 mcg, 37%; and FF 100 mcg, 37%
  - HZA-714: FF/VI 200/25 mcg, 26%; and FP 500 mcg, 27%
  - HZA-829: FF/VI 200/25 mcg, 47%; FF 200 mcg, 46%; and FP 500 mcg, 50%
  - HZA-091: FF/VI 100/25 mcg, 53%; and FP/S 250/50 mcg, 49%
  - HZA-837: FF/VI 100/25 mcg, 63%; and FF 100 mcg, 65%
  - HZA-839: FF/VI 200/25 mcg, 66%; FF/VI 100/25 mcg, 69%; and FP 500 mcg, 73%.
- The proportions of patients with at least one serious adverse event were:
  - HZA-827: FF/VI 100/25 mcg, 0%; FF 100 mcg, < 1%; and placebo, 0%
  - HZA-863: FF/VI 200/25 mcg, < 1%; FF/VI 100/25 mcg, 1%; and FF 100 mcg, < 1%
  - HZA-714: FF/VI 200/25 mcg, < 1%; and FP 500 mcg, 1%
  - HZA-829: FF/VI 200/25 mcg, 3%; FF 200 mcg, < 1%; and FP 500 mcg, 1%
  - HZA-091: FF/VI 100/25 mcg, < 1%; and FP/S 250/50 mcg, 1%
  - HZA-837: FF/VI 100/25 mcg, 4%; and FF 100 mcg, 3%
  - HZA-839: FF/VI 200/25 mcg, < 1%; FF/VI 100/25 mcg, 1%; and FP 500 mcg, 7%.
- The proportions of patients who withdrew as a result of adverse events were:
  - HZA-827: FF/VI 100/25 mcg, < 1%; FF 100 mcg, 0%; and placebo, < 1%
  - HZA-863: FF/VI 200/25 mcg, < 1%; FF/VI 100/25 mcg, < 1%; and FF 100 mcg, 1%
  - HZA-714: FF/VI 200/25 mcg, 1%; and FP 500 mcg, 1%
  - HZA-829: FF/VI 200/25 mcg, 4%; FF 200 mcg, 2%; and FP 500 mcg, 1%
  - HZA-091: FF/VI 100/25 mcg, 1%; and FP/S 250/50 mcg, 2%
  - HZA-837: FF/VI 100/25 mcg, 2%; and FF 100 mcg, 2%
  - HZA-839: FF/VI 200/25 mcg, 1%; FF/VI 100/25 mcg, 2%; and FP 500 mcg, 6%.

Cost and Cost-Effectiveness

The manufacturer submitted a cost analysis comparing FF/VI with other ICS/LABA combination products, for the maintenance treatment of asthma in patients aged 18 years and older with reversible obstructive airways disease. The comparators included budesonide/formoterol fumarate (BUD/F), FP/S, and mometasone furoate/formoterol fumarate (MOM/F). Specifically, FF/VI 100/25 mcg was compared with a claims-based weighted average cost of low- and medium-dose ICS/LABA combination therapies and FF/VI 200/25 mcg was compared with a claims-based weighted average cost of high-dose ICS/LABA combination therapies. The analysis considered only drug costs on a daily and one-year time horizon — it was assumed that other resource use components were equal between comparators, based on the assumption of similar efficacy and safety of FF/VI and other ICS/LABA combination products. This assumption was based on HZA-091 and a manufacturer-submitted network meta-analysis (NMA).

CDR noted the following limitations with the manufacturer's pharmacoeconomic submission:

- There was uncertainty regarding the comparative efficacy and safety of FF/VI versus other ICS/LABA combination therapies, due to the limitations of HZA-091 and the NMA.
- There are limitations with the claims-based utilization data that were used (e.g., inability to differentiate claims for children and adolescents and adults, or by indication), where it would be more appropriate to compare FF/VI with individual ICS/LABA combination therapies.
- The comparison of FF/VI 100/25 mcg to low-dose ICS/LABA combination therapies is inappropriate, given that FF/VI 100/25 mcg is a medium-dose ICS/LABA.

At recommended daily doses, FF/VI 100 mcg/25 mcg ([redacted] per day) is less costly than other medium-dose ICS/LABA combination therapies ($2.80 to $3.25 per day) and FF/VI 200/25 mcg ([redacted] per day) is less costly than other high-dose ICS/LABA combination therapies ($3.62 to $5.59 per day).

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- Direct comparisons of FF/VI against ICS/LABA combinations other than FP/S
- The longer-term safety and efficacy of FF/VI in the treatment of asthma requires further evaluation.

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.

January 20, 2016 Meeting

Regrets:

None

Conflicts of Interest:

One CDEC member did not vote due to a conflict of interest.

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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