CDEC CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

FLUTICASONE FUROATE
(Arnuity Ellipta — GlaxoSmithKline Inc.)
Indication: Asthma

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that fluticasone furoate (FF) be listed for the once-daily maintenance treatment of steroid-responsive bronchial asthma in patients aged 12 years and older, if the following condition is met:

Condition
- Drug plan cost for FF should not exceed the drug plan cost of the least expensive inhaled corticosteroid (ICS) reimbursed by the jurisdiction.

Reasons for the Recommendation:
1. Four double-blind randomized controlled trials (RCTs) demonstrated that FF was superior to placebo and one RCT demonstrated that FF was non-inferior to fluticasone propionate (FP) for improving lung function in patients with severe asthma.
2. At the submitted price ([redacted]), FF is less costly than FP ($1.38 to $2.14 per day) at comparable dosages. Depending on the dosage and product, FF can be less costly, similar in cost, or more costly than other ICSs ($0.31 to $2.75).

Background:
FF is a corticosteroid with anti-inflammatory properties, administered by oral inhalation via a novel dry powder inhaler. At the recommended once-daily dose of 100 mcg to 200 mcg per day, FF is indicated for the maintenance treatment of steroid-responsive bronchial asthma in patients aged 12 years or older.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs and pivotal studies of fluticasone, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients living with asthma.

Patient Input Information

The Asthma Society of Canada and the National Asthma Patient Alliance jointly responded to the CDR call for patient input. Information was obtained from an online survey that targeted asthma patients and their caregivers. The following is a summary of information provided by the patient groups:

- Asthma can negatively affect many aspects of patients' lives, and those who are affected can have limited ability to participate in physical activity and exercise, and experience sleep disturbances, absences from work or school, stress associated with the stigma of having asthma, and concern about the impact of the condition on their caregivers.
- Patients indicated that the important considerations for asthma treatments include the need to control symptoms and limit exacerbations, the dosing frequency, and the cost of the treatment.
- Patients reported having experience with a range of different therapeutic options and indicated that there remains a significant unmet need for medications that can effectively control symptoms, with limited side effects.

Clinical Trials

The CDR systematic review included five active-controlled, double-blind, parallel-group RCTs: FFA-687 (N = 601), HZA-827 (N = 610), HZA-829 (N = 587), FFA-059 (343), and FFA-496 (N = 239). The included studies compared the efficacy of FF with that of FP, the combination of fluticasone furoate and vilanterol (FF/VI), different FF doses, and/or placebo. One study (HZA-829) evaluated the non-inferiority of FF 200 mcg daily compared with FP 500 mcg twice daily. The patient populations differed from one study to another in terms of pre-study asthma medication use.

Outcomes

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

- Forced expiratory volume in one second (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 symptom-free days and rescue-free days.

The primary outcome of all studies was change from baseline in trough evening FEV_1, which was recorded before the use of a bronchodilator or the study medication dose. Two studies, HZA-827 and HZA-829, specified weighted mean serial FEV_1 as a co-primary outcome.

Efficacy

- FF 100 mcg and 200 mcg were associated with a statistically significant increase in symptom-free days compared with placebo in studies FFA-687 and FFA-059; however, the difference between FF 100 mcg and placebo was not statistically significant in HZA-827. Treatment with FF/VI was associated with more symptom-free days than FF. Mean differences between groups were reported as follows:

  - FF 100 mcg versus placebo: 20.2 days ($P < 0.001$) in FFA-687, 5.8 days ($P = 0.055$) in HZA-827, and 8.9 days ($P = 0.025$) in FFA-059
  - FF 200 mcg versus placebo: 13.2 days ($P < 0.004$) in FFA-687
  - FF 100 mcg versus FF/VI 100 mcg/25 mcg: −12.1 days ($P = 0.001$) in HZA-827
  - FF 200 mcg versus FF/VI 200 mcg/25 mcg: −8.4 days ($P = 0.01$) in HZA-829.
- FF 200 mcg was non-inferior to FP for improvement in FEV_1 in FFA-687. Both doses of FF were associated with a statistically significant improvement in FEV_1 compared with placebo. Both doses of FF/VI were associated with statistically significant improvement in FEV_1 compared with FF. Mean differences between groups were reported as follows:
  - FF 100 mcg versus placebo: 0.20 L ($P < 0.001$) in FFA-687, 0.136 L ($P = 0.002$) in HZA-827, and 0.15 L ($P = 0.009$) in FFA-059
  - FF 200 mcg versus placebo: 0.23 L ($P < 0.001$) in FFA-687
  - FF 200 mcg versus FP 500 mcg: 0.018 L (95% confidence interval [CI], −0.066 to 0.102) in HZA-829
  - FF 100 mcg versus FF/VI 100 mcg/25 mcg: −0.04 ($P = 0.405$) in HZA-827
  - FF 200 mcg versus FF/VI 200 mcg/25 mcg: −0.19 ($P < 0.001$) in HZA-829.
- Compared with placebo, FF was associated with a statistically significant improvement in PEF in FFA-687 and HZA-827, but not in FFA-059. FF/VI was associated with a statistically significantly greater change in PEF compared with FF. Mean differences between groups were reported as follows:
  - FF 100 mcg versus placebo: 16.1 L/min ($P = 0.005$) in FFA-687, 15.9 L/min ($P < 0.001$) in HZA-827, and 2.8 L/min ($P = 0.564$) in FFA-059
  - FF 200 mcg versus placebo: 21.7 L/min ($P < 0.001$) in FFA-687
  - FF 200 mcg versus FF 100 mcg: −1.3 L/min (95% CI, −7.8 to 10.4) in HZA-496
  - FF 100 mcg versus FF/VI 100 mcg/25 mcg: −12.3 L/min ($P = 0.001$) in HZA-827
  - FF 200 mcg versus FF/VI 200 mcg/25 mcg: −30.7 L/min ($P < 0.001$) in HZA-829.
- There was inconsistency in the results for changes in AQLQ +12 scores across the trials. FF 100 mcg was associated with a statistically significant improvement compared with placebo in FFA-059, but not in HZA-827. FF/VI was statistically superior to FF in HZA-827, but not in HZA-829. Mean differences in change from baseline in AQLQ +12 were reported as follows:
  - FF 100 mcg versus placebo: 0.15 ($P = 0.073$) in HZA-827 and 0.33 ($P = 0.007$) in FFA-059
  - FF 100 mcg versus FF/VI 100 mcg/25 mcg: −0.15 ($P = 0.059$) in HZA-827
  - FF 200 mcg versus FF/VI 200 mcg/25 mcg: −0.05 ($P = 0.59$) in HZA-829.
- All treatment groups in the included studies showed an increase in the percentage of rescue-free days relative to baseline. FF 100 mcg and 200 mcg were associated with statistically significant increases in the percentage of rescue-free days. FF/VI was associated with a greater percentage of rescue-free days than FF.
  - FF 100 mcg versus placebo: 18.9 ($P < 0.001$) in FFA-687, 8.7 ($P = 0.007$) in HZA-827, and 14.8 ($P < 0.001$) in FFA-059
  - FF 200 mcg versus placebo: 10.1 ($P = 0.031$) in FFA-687
  - FF 100 mcg versus FF/VI 100 mcg/25 mcg: −10.6 ($P < 0.001$) in HZA-827
  - FF 200 mcg versus FF/VI 200 mcg/25 mcg: −11.7 ($P < 0.001$) in HZA-829.

Harms (Safety and Tolerability)

- The proportions of patients with at least one serious adverse event were:
  - FFA-687: FF 100 mcg, 1%; FF 200 mcg, 0%; FP 100 mcg, 2%; and placebo, 0%

  - HZA-827: FF 100 mcg, < 1%; FF/VI 100 mcg/25 mcg, 0%; and placebo, 0%
  - HZA-829: FF 200 mcg, < 1%; FF/VI 200 mcg/25 mcg, 3%; and FP 500 mcg, 1%.
- The most frequently reported adverse events were bronchitis (0% to 12%), headache (4% to 13%), and nasopharyngitis (1% to 20%). Similar rates of adverse events were reported with FF compared with the other active treatments. The proportions of patients who experienced at least one adverse event were:
  - FFA-687: FF 100 mcg, 32%; FF 200 mcg, 28%; FP 100 mcg, 34%; and placebo (26%)
  - HZA-827: FF 100 mcg, 25%; FF/VI 100 mcg/25 mcg, 29%; and placebo, 21%
  - HZA-829: FF 200 mcg, 46%; FF/VI 200 mcg/25 mcg, 47%; and FP 500 mcg, 50%
  - FFA-059: FF 100 mcg, 53%; FP 250 mcg, 42%; and placebo, 40%.
- The proportions of patients who withdrew as a result of adverse events were:
  - FFA-687: FF 100 mcg, 2%; FF 200 mcg, 1%; FP 100 mcg, 2%; and placebo, 0%
  - HZA-827: FF 100 mcg, 0%; FF/VI 100 mcg/25 mcg, < 1%; and placebo, < 1%
  - HZA-829: FF 200 mcg, 2%; FF/VI 200 mcg/25 mcg, 4%; and FP 500 mcg, 1%
  - FFA-059: FF 100 mcg, 3%; FP 250 mcg, 3%; and placebo, 2%.

Cost and Cost-Effectiveness

The manufacturer submitted a cost comparison of FF with FP and a weighted claims average of ICSs (including FP, ciclesonide, mometasone furoate, budesonide [BUD], and beclomethasone) over a one-year time horizon. Specifically, FF 100 mcg daily was compared with FP 250 mcg twice daily, and weighted claims averages of low- or medium-dose ICS monotherapies; and FF 200 mcg daily was compared with FP 500 mcg twice daily, and a weighted claims average of high-dose ICS monotherapies. The manufacturer assumed similar clinical efficacy and harms for FF compared with FP, based on manufacturer-sponsored trials (FFA-059 and HZA-829), and with ICS monotherapies based on a published systematic review.

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

- No head-to-head evidence was provided that compared FF 100 mcg per day with FP 250 mcg twice daily.
- The assumption of non-inferiority of FF to FP was based on a 24-week trial in which benefits appeared to plateau after 12 weeks and equivalence beyond the 24-week study period is uncertain.
- No direct or indirect evidence was provided to compare the clinical efficacy or harms of FF against ICS monotherapies other than FP.
- Cost comparisons were made based on weighted claims averages, whereas individual comparisons would have been most appropriate.

At recommended doses, the cost of FF ([redacted]) is less than FP (FP 250 mcg twice daily, $1.38; FP 500 mcg twice daily, $2.14) at respective low/high doses.

While the assessment of FF with other ICS monotherapies is limited by the lack of comparative clinical studies to establish dose equivalence, similar harms, and clinical efficacy, CDR presented comparative daily cost information on low, medium, and high doses. When compared with low-dose ICSs, the cost of FF 100 mcg is greater ([redacted] compared with $0.31 to $0.80 per day); when compared with medium-dose ICSs, the cost of FF 100 mcg is the [redacted] (800 mcg per day; $0.93), but lower than other medium-dose ICSs ($1.18 to $1.38 per day); when compared with high-dose ICSs, FF 200 mcg ([redacted]) is more costly than BUD (1,200 mcg per day; $1.40), but less costly than other high-dose ICSs ($1.87 to $2.75 per day).

Other Discussion Points:
CDEC noted the following:

- The Health Canada–approved indication for FF is limited to patients who are aged 12 years and older.
- The place in therapy for ICS products is influenced by differences in the devices used to deliver the medication, the potency of the corticosteroids, and the possibility that the dose can be adjusted.
  - There is limited comparative evidence regarding the ease of use for the Ellipta device compared with alternative ICS inhalers.
  - There were insufficient data to establish the equivalent doses of different ICS, which introduces uncertainty when evaluating the comparative cost of the products.
  - Some ICS inhalers allow the dosage to be adjusted in response to changing symptoms (e.g., as a result of allergies or a viral infection). The Ellipta inhaler does not allow the dosage of FF to be adjusted; however, patients could increase the number of actuations per day to increase their daily dosage.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- None of the included RCTs were designed or powered to assess treatment differences in chronic obstructive pulmonary disease (COPD) exacerbations.
- COPD is a chronic condition and all of the included RCTs were short-term studies.
- The included studies did not report on growth rate in adolescents or potential adrenal suppression.

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.

November 18, 2015 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*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer.