



## CDEC FINAL RECOMMENDATION

### (FLUTICASONE FUROATE/VILANTEROL)

#### (Breo Ellipta — GlaxoSmithKline)

#### Indication: Chronic Obstructive Pulmonary Disease

#### Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that fluticasone furoate/vilanterol (FF/V) be listed for the long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and to reduce exacerbations of COPD in patients with a history of exacerbations, if the following clinical criteria are met:

#### Clinical Criteria:

- Moderate to severe COPD as defined by spirometry.
- Inadequate response to a long-acting bronchodilator (long-acting beta-2 agonist [LABA]/long-acting muscarinic antagonist [LAMA]) or experiencing exacerbations more than once per year while on a long-acting bronchodilator.

#### Reasons for the Recommendation:

1. Five randomized controlled trials (RCTs) demonstrated that FF/V was similar to tiotropium (TIO) and fluticasone propionate/salmeterol (FP/S) for improving forced expiratory volume in one second (FEV<sub>1</sub>) in patients with moderate to severe COPD.
2. At the submitted price (100 mcg/25 mcg once daily; \$█████ per day), FF/V is less costly than FP/S (250 mcg/50 mcg to 500 mcg/50 mcg twice daily; \$3.25 to \$4.61 per day) and ██████ budesonide/formoterol (400 mcg/12 mcg twice daily; \$2.76 per day).

#### Of Note:

CDEC noted that the listing status of LABA/inhaled corticosteroid (ICS) products varies across the CDR-participating drug plans.

#### Background:

Breo-Ellipta (FF/V) is a combination of an ICS, fluticasone furoate, and a LABA, vilanterol. FF/V is indicated for the long-term, once-daily maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema, and to reduce exacerbations of COPD in patients with a history of exacerbations. FF/V is available as a dry powder for oral inhalation (100 mcg/25 mcg) and the recommended dose is one inhalation once daily.

## Common Drug Review

### Summary of CDEC Considerations

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of FF/V, a critique of the manufacturer's pharmacoeconomic evaluation, and a summary of patient group-submitted information about outcomes and issues important to individuals living with COPD.

### Patient Input Information

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

- COPD is a debilitating condition that worsens over time and those living with the disease have difficulty breathing and performing activities of daily living. Lung infections and exposure to humidity and air pollution can have a worsening effect on symptoms.
- The patient group noted that currently available therapies may slow the progressive loss of lung function; however, they do not prevent COPD exacerbations. This is an important concern as exacerbations may cause permanent reductions in lung health and function, resulting in a greater dependence on caregivers and the health care system.
- Additional treatments are needed that will help maintain lung function in COPD and prevent exacerbations of the disease.

### Clinical Trials

The CDR systematic review included the following 10, double-blind, multi-centre RCTs:

- Active-controlled studies: four 12-week RCTs compared FF/V against FP/S (studies 6974 [N = 828], 3107 [N = 528], 2352 [N = 511], and 3109 [N = 519]) and one 12-week RCT compared FF/V against TIO (study 5805 [N = 623]).
- Placebo-controlled studies: two 24-week RCTs (study 2206 [N = 1,030] and 2207 [N = 1,224]) were identically designed, parallel-group studies and one RCT (study 946 [N = 84]) was a small crossover study.
- Vilanterol-controlled studies: two RCTs (studies 2871 [N = 1,622] and 2970 [N = 1,633]) compared FF/V to vilanterol during a treatment period of 52 weeks.

As vilanterol is not marketed as a stand-alone product in Canada, CDEC focused their deliberations on the active-controlled studies (i.e., FP/S and TIO) and the placebo-controlled studies.

### Outcomes

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

- FEV<sub>1</sub> — the volume of air that, after a full inspiration, can be forcibly expired in one second. Changes in FEV<sub>1</sub> were assessed using the following measurements:
  - change from baseline in 0 to 24-hour weighted-mean FEV<sub>1</sub>
  - change from baseline in 0 to 4-hour weighted-mean FEV<sub>1</sub>
  - change from baseline in trough FEV<sub>1</sub>.
- St. George's Respiratory Questionnaire (SGRQ) — a 50-item questionnaire that measures distress due to respiratory symptoms, mobility and physical activity, and the psychosocial impact of the disease.
- Chronic Respiratory Questionnaire – Self-Administered Scale (CRQ-SAS) — a questionnaire consisting of 20 items measuring four domains: dyspnea, fatigue, emotional

function, and mastery. Patients rated their experience on a 7-point scale where a higher score indicates less severe symptoms or better quality of life.

- COPD exacerbations defined as an acute worsening of COPD symptoms requiring the use of any treatment other than study medication or rescue albuterol (salbutamol). This included using antibiotics, systemic corticosteroids, and/or emergency treatment or hospitalization. Exacerbation severity was reported as:
  - Severe: required hospitalization.
  - Moderate: required treatment with antibiotics and/or systemic corticosteroids.
  - Mild: self-managed, and did not require use of oral corticosteroids or antibiotics.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

Change from baseline in 24-hour weighted-mean FEV<sub>1</sub> on day 84 was the primary outcome of all active-controlled studies and the placebo-controlled crossover study. In studies 2206 and 2007 the FEV<sub>1</sub> (0 to 4 h) and trough FEV<sub>1</sub> were the co-primary outcomes.

### ***Efficacy***

#### Active-controlled studies

- There was no statistically significant difference in FEV<sub>1</sub> (0 to 24-hour weighted mean) between FF/V and TIO in study 5805 and between FF/V and FP/S in studies 3107, 2352, and 6974. There was a statistically significant difference favouring FF/V compared with FP/S (250 mcg/50 mcg) in study 3109 (P < 0.001). The least-square mean difference (LS MD) in FEV<sub>1</sub> (0 to 24 h weighted mean) was reported as follows:
  - FF/V versus FP/S (500 mcg/50 mcg): 0.022 L (95% CI, -0.022 L to 0.063 L) in study 3107.
  - FF/V versus FP/S (250/50): 0.025 L (95% CI, -0.008 to 0.059) in study 6974, 0.080 L (95% CI, 0.037 L to 0.124 L) in study 3109, and 0.029 L (95% CI, -0.022 L to 0.080 L) in study 2352.
  - FF/V versus TIO: 0.022 L (95% CI, -0.012 L to 0.055 L) in study 5805.
- There was no statistically significant difference between FF/V and FP/S or between FF/V and TIO in trough FEV<sub>1</sub>. The LS MD in trough FEV<sub>1</sub> was reported as follows:
  - FF/V versus FP/S (500 mcg/50 mcg): 0.023 L (-0.020 L to 0.066 L) in study 3107.
  - FF/V versus FP/S (250 mcg/50mcg): 0.030 L (-0.005 L to 0.065 L) in study 6974.
  - FF/V versus TIO: 0.005 L (-0.029 L to 0.039 L) in study 5805.
- There was no statistically significant difference in change from baseline in SGRQ total score when FF/V was compared with FP/S or TIO. The LS mean change in SGRQ total score was reported as follows:
  - FF/V versus FP/S (500 mcg/50 mcg): -1.5 (95% CI, -3.9 to 0.9) in study 3107.
  - FF/V versus TIO: [REDACTED] in study 5805.
- There were a similar number of exacerbations between the FF/V and FP/S groups in study 3107 and study 6974 and between FF/V and TIO in study 5805. No statistical analyses were provided in any of these studies. All of the exacerbations were reported as having resolved, and the majority were resolved using oral steroids.
- There was a [REDACTED]

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## Common Drug Review

Placebo-controlled studies

- FF/V was superior to placebo for changes from baseline in FEV<sub>1</sub> in studies 2206, 2207, and 946.
  - FEV<sub>1</sub> (0 to 4-hour weighted mean): 0.173 L (95% CI, 0.123 L to 0.224 L) in study 2206 and 0.214 L (95% CI, 0.161 L to 0.266 L) in study 2207.
  - Trough FEV<sub>1</sub>: 0.115 L (95% CI, 0.060 L to 0.169 L) in study 2206, [REDACTED] in study 2207, and 0.177 L (95% CI, 0.097 L to 0.257 L) in study 946.
  - FEV<sub>1</sub> (0 to 24-hour weighted mean): 0.220 L (95% CI, 0.165 L to 0.275 L) in study 946.
- FF/V was superior to placebo for changes from baseline in CRQ-SAS total score and dyspnea score in studies 2206 and 2207:
  - [REDACTED]
  - CRQ-SAS (dyspnea): 0.30 (95% CI, 0.06 to 0.54) in study 2206 and 0.24 (95% CI, 0.02 to 0.46) in study 2207.
- FF/V was superior to placebo for changes in symptom scores in studies 2206 and 2207:
  - [REDACTED]
  - [REDACTED]
  - [REDACTED]

**Harms (Safety and Tolerability)**

- The proportion of patients who experienced at least one adverse event was reported as follows:
  - FF/V versus TIO: 36% with FF/V and 32% with TIO in study 5805.
  - FF/V versus placebo: 54% with FF/V and 48% with placebo in study 2206; 45% with FF/V and 47% with placebo in study 2207.
  - FF/V versus FP/S: 27% with FF/V and 26% with FP/S in study 3107; 32% with FF/V and 33% with FP/S in study 6974; 20% with FF/V and 23% with FP/S in study 2352; 25% with FF/V and 25% with FP/S in study 3109.
- The proportion of patients who experienced at least one serious adverse event was reported as follows:
  - FF/V versus TIO: 3% in both groups in study 5805.
  - FF/V versus placebo: 5% in both groups in study 2206; FF/V versus placebo: 6% with FF/V and 5% with placebo in study 2207.
  - FF/V versus FP/S: 2% with FF/V and 1% with FP/S in study 3107; 3% with FF/V and 5% with FP/S in study 6974; 2% with FF/V and 1% with FP/S in study 2352; 1% with FF/V and 3% with FP/S in study 3109.
- The proportion of patients who withdrew as a result of adverse events was reported as follows:
  - FF/V versus TIO: [REDACTED]
  - FF/V versus placebo: 7% in both groups in study 2206; 8% with FF/V and 9% with placebo in study 2207.

- FF/V versus FP/S: 2% with FF/V and 1% with FP/S in study 3107; 3% with FF/V and 4% with FP/S in study 6974; 2% with FF/V and <1% with FP/S in study 2352; 2% with FF/V and 3% with FP/S in study 3109.

### **Cost and Cost-Effectiveness**

The manufacturer submitted a cost-minimization analysis comparing FF/V 100 mcg/25 mcg with FP/S 250 mcg/50 mcg and 500 mcg/50 mcg in adult patients with moderate to severe COPD, with FEV<sub>1</sub> ≤ 70% predicted post-bronchodilator, during a five-year time horizon. Equivalent efficacy and safety were assumed between treatments based on head-to-head clinical trials. CDR noted the following limitations with the manufacturer's pharmacoeconomic evaluation:

- the manufacturer acknowledged that budesonide/formoterol, the other available LABA/ICS combination product, would ideally have been incorporated into their economic analysis
- the assumption of clinical equivalence to FP/S is based on 12-week trials and may not persist over the five-year analysis period.

At the submitted price of \$█████ per 30-actuation inhaler (100 mcg/25 mcg daily; \$█████ per day), FF/V is less costly than FP/S (250 mcg/50 mcg to 500 mcg/50 mcg twice daily; \$3.25 to \$4.61 per day). FF/V is ██████ budesonide/formoterol (400 mcg/12 mcg twice daily; \$2.76 per day), but more costly than the three long-acting anticholinergics available in Canada (\$1.77 to \$2.35 per day), which were not considered as comparators by the manufacturer. FF/V is also more costly than combination therapy with budesonide and formoterol administered individually (\$2.41 to \$2.57 per day).

### **Other Discussion Points:**

CDEC noted the following:

- The once-daily dosing of FF/V may be advantageous for patients when compared with the twice daily dosing regimens recommended for other ICS/LABA combinations.
- Neither fluticasone furoate nor vilanterol is approved as a separate inhaler in Canada; therefore, the progression of starting the patient on a LABA and adding an ICS would require that the patient switch LABAs, which may not be optimal for patient care.
- Similar to the product monograph for FP/S, the product monograph for FF/V states that an increase in the incidence of pneumonia has been observed in patients with COPD receiving treatment with the LABA/ICS combination. The RCTs included in the CDR systematic review were too short in duration and lacked statistical power to draw any conclusions about the comparative risk of pneumonia with FF/V relative to FP/S.

### **Research Gaps:**

CDEC noted that there is an absence of evidence regarding the following:

- No trials directly comparing FF/V against budesonide/formoterol (Symbicort).
- No trials directly comparing FF/V against other ICS/LABAs for differences in exacerbation rates or long-term COPD-related morbidity and mortality.
- Longer-term studies are required to characterize the risk of pneumonia in patients treated with FF/V and other LABA/ICS products.

**CDEC Members:**

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

**July 16, 2014 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 in conformity with the *CDR Confidentiality Guidelines*.

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