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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

FLUTICASONE FUROATE/UMECLIDINIUM/VILANTEROL (TRELEGY ELLIPTA — GLAXOSMITHKLINE plc)

Indication: Maintenance treatment of chronic obstructive pulmonary disease (COPD)

RECOMMENDATION

The CADTH Canadian Drug Expert Committee (CDEC) recommends that fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) be reimbursed for the long-term, once daily, maintenance treatment of COPD, including chronic bronchitis and/or emphysema, if the following criteria and condition are met:

Criteria

- Patients should not be started on triple inhaled therapy as initial therapy for COPD.
- For use in patients who are not controlled on optimal dual-inhaled therapy for COPD.

Condition

- Drug plan cost of FF/UMEC/VI should not exceed the drug plan cost of treatment with any triple therapies reimbursed for COPD (long-acting muscarinic antagonist [LAMA]/long-acting beta-2 agonist [LABA]/inhaled corticosteroid [ICS]).

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Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) be reimbursed for the long-term, once daily, maintenance treatment of COPD, including chronic bronchitis and/or emphysema, if the following criteria and condition are met:

Criterion

- Patients should not be started on triple inhaled therapy as initial therapy for COPD.
- For use in patients who are not controlled on optimal dual inhaled therapy for COPD.

Condition

- The drug plan cost of FF/UMEC/VI should not exceed the drug plan cost of treatment with any triple therapies reimbursed for COPD (long-acting muscarinic antagonist [LAMA]/long-acting beta-2 agonist [LABA]/inhaled corticosteroid [ICS]).

Reasons for the Recommendation:

1. Two multi-centre, double-blind, randomized controlled trials (RCTs) (FULFIL [N = 1,810] and IMPACT [10,355]) demonstrated that FF/UMEC/VI was associated with a statistically significant improvement in the rate of moderate-to-severe exacerbations, and improved pulmonary function (as measured using trough forced expiratory volume in one second [FEV_1]) as compared with budesonide/formoterol (BUD/FOR; FULFIL) at 24 weeks, and as compared with FF/VI and UMEC/VI at 52 weeks (IMPACT).
2. One double-blind, non-inferiority RCT (Study 200812 [N = 1,055]) demonstrated that FF/UMEC/VI was non-inferior to FF/VI plus UMEC for improving pulmonary function (as measured by FEV_1) at 24 weeks.
3. At the manufacturer-submitted price of $132.20 per 30 doses ($4.41 daily or $1,608 annual average cost per patient), FF/UMEC/VI is likely to be cost-effective compared with dual therapies (i.e., FF/VI and UMEC/VI), but there is significant uncertainty around the cost-effectiveness of FF/UMEC/VI compared with other triple therapies. There is no evidence that the combination of FF/UMEC/VI is clinically superior to other combinations of LAMA/LABA/ICS.

Of Note:

- Recommendations from the Canadian Thoracic Society and the Global Initiative for Chronic Obstructive Lung Disease generally recommend inhaled LAMA/LABA dual therapy as the preferred regimen for most patients with stable COPD experiencing exacerbations, persistent or increased symptoms, exercise intolerance, and/or reduced health status despite the use of LAMA or LABA monotherapy. Clinician expert input indicated that step-up to triple therapy with LAMA/LABA/ICS is currently considered in patients with recurrent exacerbations despite dual bronchodilator therapy.
- CDEC noted, with clinician expert input, that there is concern regarding the overuse of ICS — in combination with a LABA — in the management of patients with stable COPD. It particularly noted concerns that ICS is associated with an increased risk for developing pneumonia and systemic adverse effects. CDEC noted that the increased risk of pneumonia associated with FF/UMEC/VI was not accounted for in the economic analysis.
- Step-down from triple therapy with FF/UMEC/VI to LAMA/LABA dual therapy may be considered in patients who are not experiencing exacerbations or who are having infrequent and only mild exacerbations; or in patients who are experiencing adverse effects that negate any benefits from triple therapy. There is uncertainty as to the optimal timing to assess treatment step-down; however, clinician expert input suggested step-down could be considered between one and two years of treatment with FF/UMEC/VI.

Discussion Points:

- CDEC noted that the clinical evidence of relative effectiveness and economic information for FF/UMEC/VI versus other triple therapies is highly uncertain.
- CDEC discussed, with clinician expert input, the role of pharmacotherapy step-up and step-down in the management of COPD. CDEC noted that step-down allows physicians to review patient stability and to minimize pharmacological treatments, especially given the potential risk of serious adverse events related to treatment (e.g., increased risk of pneumonia with ICS use).

Background:

FF/UMEC/VI has a Health Canada indication for long-term, once daily, maintenance treatment of COPD, including chronic bronchitis and/or emphysema in patients who are not adequately treated by a combination of an ICS/LABA. FF/UMEC/VI is the first inhaled triple combination therapy composed of an ICS (FF), a LABA (VI), and a LAMA (UMEC). It is available as dry powder for oral inhalation and the Health Canada–approved dose is 100 mcg/62.5 mcg/25 mcg.

Summary of CDEC Considerations:

The Committee considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs, a manufacturer-provided indirect comparison, and a critique of the manufacturer's pharmacoeconomic evaluation. The Committee also considered input from a clinical expert with experience in diagnosing and treating patients with COPD, and patient group-submitted information about outcomes and issues important to patients and caregivers.

Patient Input Information:

COPD Canada provided input for this submission. Patient and caregiver perspectives were obtained from an email survey, one-on-one consultations, lung issue support groups, and pulmonary rehabilitation sessions. The following is a summary of key input from the perspective of the patient group:

- COPD affects almost all aspects of daily living, such as the ability to breath, talk, sleep, work, and socialize. As the disease progresses and worsens, patients become less physically active and more socially isolated.
- Caregivers face considerable challenges that commonly include: limited time for managing their health and well-being; feelings of depression and isolation; anxiety, stress, fatigue; a feeling of unending days; and increased requirements for social support.
- Exacerbations are a concern for patients, as they are associated with both short- and long-term consequences on overall health, such as a decline in lung function, greater anxiety, worsening quality of life, social withdrawal, more exacerbations, and increased risk of hospitalization and mortality.
- Current therapies for COPD provide some relief of symptoms, but their effectiveness diminishes over time. A variety of adverse effects, which patients find problematic, are associated with these medications.
- Patients are looking for drugs that can improve lung function and quality of life, reduce exacerbations, delay disease progression, and improve survival. Patients indicated that the diminishing effectiveness with the long-term use of some medications should be addressed, and that therapies that offer a convenient treatment option for COPD patients who require long-term maintenance therapy are desirable.

Clinical Trials

The CDR systematic review included three phase III RCTs of patients with COPD. FULFIL (N = 1,810) randomized patients in a 1:1 ratio (double-blind and double-dummy fashion) to treatment with FF/UMEC/VI 100 mcg/62.5 mcg/25 mcg via the Ellipta inhaler once daily, or to treatment with BUD/FOR 400 mcg/12 mcg via the Turbuhaler inhaler twice daily for 24 weeks. A subset of the first 430 patients randomized could continue in their assigned treatment groups into an extension study to receive a total of 52 weeks of treatment. IMPACT (N = 10,355) randomized patients in a 2:2:1 ratio to once daily treatment with FF/UMEC/VI 100 mcg/62.5 mcg/25 mcg, or FF/VI 100 mcg/25 mcg, or UMEC/VI 62.5 mcg/25 mcg, respectively, for 52 weeks. Study 200812 (N = 1,055) was a non-inferiority trial that randomized patients in a 1:1 ratio to treatment with FF/UMEC/VI 100 mcg/62.5 mcg/25 mcg once daily, or to

treatment with FF/VI 100 mcg/25 mcg once daily plus UMEC 62.5 mcg once daily. All treatments and dummy placebo were administered via the Ellipta inhaler.

Limitations with the reviewed studies included: the statistical analyses of secondary outcome measures in FULFIL were not adjusted for multiplicity; only one of the studies (IMPACT) was designed to evaluate exacerbations as a primary outcome; the comparators used in two of the three studies were components of FF/UMEC/VI, and ICS/LABA was the comparator in the third study (FULFIL) and therefore there is limited data comparing FF/UMEC/VI with LAMA/LABA combinations (other than UMEC/VI) and with other inhaled triple therapies for COPD.

Outcomes

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

- pulmonary function as measured using the change from baseline in trough FEV_1. The generally accepted minimal clinically important difference (MCID) for trough FEV_1 ranges from 0.10 L and 0.14 L.
- health-related quality of life as measured using the change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score. A higher score (on a scale from 0 to 100) on the SGRQ indicates a poorer level of health-related quality of life and decreases in the score are indicative of improvement in health-related quality of life. A decrease of four points from baseline is considered the MCID.
- the annual rate of on-treatment moderate-to-severe exacerbations. A moderate exacerbation was defined as requiring treatment with oral and systemic corticosteroids and/or antibiotics (not involving hospitalization). A severe exacerbation required in-patient hospitalization.
- the Transition Dyspnea Index (TDI) focal score. The TDI measures changes in dyspnea severity from the baseline as established by the baseline dyspnea index. The TDI consists of 24 items which are graded; lower scores indicate more deterioration related to an increase in severity of dyspnea from baseline. The range of the TDI focal score is –9 to +9. A change in one point is considered clinically meaningful.
- Health status was measured using the COPD assessment test (CAT). The CAT consists of eight items that address the following: cough, phlegm, chest tightness, breathlessness going up a hill or stairs, activity limitation at home, confidence in leaving home, sleep, and energy. The total scale score ranges from 0 to 40 units, where higher scores represent worse health. The reported MCID for the CAT ranges from 2 to 4 units.
- the EXAcerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms (EXACT-RS). The EXACT-RS has a score that ranges from 0 to 40, with higher scores indicating more severe symptoms. Evidence based off a single study estimated the MCID of 3.35 for the EXACT-RS.
- Harms were assessed as the occurrence of adverse events (AEs), serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and notable harms (i.e., anticholinergic events, cardiovascular events, corticosteroid effects, and pneumonia).

In FULFIL, the change from baseline in trough FEV_1 and SGRQ total score at week 24 were evaluated as a co-primary outcomes. In IMPACT, the annual rate of on-treatment moderate-to-severe exacerbations was evaluated as the primary outcome over 52 weeks. In Study 200812, the change from baseline in trough FEV_1 at week 24 was the primary outcome.

Efficacy

In FULFIL, the change from baseline in trough FEV_1 at 24 weeks for FF/UMEC/VI compared with BUD/FOR was 0.17 L (95% confidence interval [CI], 0.15 L to 0.19 L; $P < 0.001$). In IMPACT, the difference in least squares change from baseline in trough FEV_1 at 52 weeks for FF/UMEC/VI compared with FF/VI was 0.097 L (95% CI, 0.085 L to 0.109 L), and 0.054 L (95% CI, 0.039 L to 0.069 L) as compared with UMEC/VI. In Study 200812, the difference in least squares change from baseline in trough FEV_1 at 24 weeks for FF/UMEC/VI compared with FF/VI + UMEC was 0.018 L (95% CI, –0.013 L to 0.050 L) for the modified per-protocol (adherent) population, and 0.026 L (95% CI, –0.002 L to 0.053 L) in the intention-to-treat population. The improvement in FEV_1 for FF/UMEC/VI compared with FF/VI + UMEC/VI was considered non-inferior, as the lower bound of the two-sided 95% CI around the treatment difference was above the pre-specified non-inferiority margin of –0.050 L.

In IMPACT, the annualized rate of on-treatment moderate-to-severe exacerbations during the 52-week study was lower in the FF/UMEC/VI arm than in both the FF/VI and UMEC/VI arms (0.91 versus 1.07 and 1.21, respectively); the rate ratios were 0.85 (95%

CI, 0.80 to 0.90) and 0.75 (95% CI, 0.70 to 0.81) for comparisons with FF/VI and UMEC/VI, respectively. The hazard ratio for time to first on-treatment moderate-to-severe exacerbation for FF/UMEC/VI compared with FF/VI and UMEC/VI at week 52 was 0.85 (95% CI, 0.80 to 0.91) and 0.84 (95% CI, 0.78 to 0.91), respectively. In FULFIL, the annualized rate of on-treatment moderate-to-severe exacerbations during the 24-week study was lower in the FF/UMEC/VI arm than in the BUD/FOR arm (0.22 versus 0.34) and the rate ratio was 0.65 (95% CI, 0.49 to 0.86). The hazard ratio for time to first on-treatment moderate-to-severe exacerbation for FF/UMEC/VI compared with BUD/FOR at week 24 was 0.67 (95% CI 0.52 to 0.88) and, at week 52 for the extension population, the hazard ratio was 0.54 (95% CI, 0.35 to 0.83). In Study 200812, the annualized rate of exacerbations was not reported. The hazard ratio for time to first on-treatment moderate-to-severe exacerbation for FF/UMEC/VI compared with FF/VI + UMEC was 0.87 (95% CI, 0.68 to 1.12).

In FULFIL, the change from baseline in the SGRQ total score at 24 weeks for FF/UMEC/VI compared with BUD/FOR was –2.2 units (95% CI, –3.5 units to –1.0 units). In IMPACT, the difference in least squares change from baseline in SGRQ total score at 52 weeks for FF/UMEC/VI compared with FF/VI was –1.8 units (95% CI, –2.4 units to –1.1 units, and compared with UMEC/VI was –1.8 units (95% CI, –2.6 units to –1.0 units). In Study 200812, the difference in least squares change from baseline in SGRQ total score at 24 weeks for FF/UMEC/VI compared with FF/VI + UMEC was –0.906 units (95% CI, –2.540 units to 0.728 units). None of the between-group differences were considered clinically significant (MCID = 4 units).

Other efficacy outcomes — such as COPD-related respiratory symptoms, health status, and use of rescue medications — were associated with mixed results across studies and, because these were not adjusted for multiple statistical comparisons, no concrete conclusions could be drawn regarding the effect of FF/UMEC/VI on these outcomes.

Harms (Safety and Tolerability)

Within each trial, SAEs were similar across treatment arms. In FULFIL, at 24 weeks, SAEs were reported in 5% and 6% of patients in the FF/UMEC/VI and BUD/FOR arms, respectively. In IMPACT, at 52 weeks, SAEs were reported in 21% to 23% of patients in each arm. In Study 200812, at 24 weeks, SAEs were reported in 10% and 11% of patients in the FF/UMEC/VI and FF/VI + UMEC arms, respectively. The most common SAEs were related to respiratory, thoracic, and mediastinal disorders; COPD; infections and infestations; and pneumonia.

There were no meaningful differences between treatment groups across all three RCTs with respect to anticholinergic and cardiovascular AEs. The percentage of patients who experienced local corticosteroid effects were similar between treatment groups that had an ICS as part of the intervention across all three studies. Pneumonia affected each arm similarly across trials, with the exception of BUD/FOR in FULFIL, where pneumonia occurred in 0.8% of patients compared with 2.2% of patients treated with FF/UMEC/VI.

Within each trial, WDAEs were similar across treatment arms. The most common WDAE was related to respiratory, thoracic, and mediastinal disorders and affected 1% to 5% of patients across trial arms in FULFIL and IMPACT.

Indirect Treatment Comparison

The manufacturer-provided indirect comparison (network meta-analysis [NMA]) suggested [redacted]

Cost and Cost-Effectiveness

FF/UMEC/VI is available at $132.20 for 30 doses, for a daily per patient cost of $4.41 or $1,608 annually.

The manufacturer submitted a cost-utility analysis with a 25-year time horizon, conducted from a Canadian public health care payer perspective, comparing FF/UMEC/VI with two dual therapies; i.e., FF/VI and UMEC/VI and a multiple inhalation triple therapy (TIO + SAL/FP). The pharmacoeconomic submission was in the form of a decision model, which was based on a previously published series of linked epidemiological equations predicting clinical outcomes, health-related quality of life, and resource use. Treatment effect was based on the IMPACT trial for comparison with dual therapies and a manufacturer-sponsored NMA for comparison with triple therapy. The manufacturer reported that FF/UMEC/VI is more costly but associated with greater quality-adjusted life-years (QALYs) compared with dual therapies; the incremental cost-utility ratio (ICUR) for FF/UMEC/VI compared with FF/VI was $19,649 per QALY and $14,864 per QALY compared with UMEC/VI. Compared with TIO + SAL/FP, FF/UMEC/VI was found to be dominant (i.e., lower total cost and higher QALYs).

CDR identified the following key limitations of the manufacturer's submitted economic analysis:

- The predictive accuracy of the epidemiologic model in estimating long-term outcomes, particularly exacerbations and health-related quality-of life, is uncertain.
- Limited comparators were included (i.e., relevant comparators such as BUD/FOR were omitted).
- No attempt was made to identify resource use data for Canadian centres or validate resource use estimates for the Canadian setting.
- Utility values were based on an inaccurate mapping algorithm and not on observed outcomes in the IMPACT trial, which likely favours FF/UMEC/VI over comparators.
- NMA assumed the equivalence of dual therapies, used trials with significant clinical heterogeneity, and had sparse data for moderate-to-severe COPD exacerbation with sufficient trial duration (n = 2).
- The SAL/FP comparator patent has expired, so generic options could reduce drug cost.

In CADTH re-analyses, when accounting for the potential generic availability of SAL/FP by setting the price equal to BUD/FOR and using an appropriate cost of physician home visits, the ICUR for FF/UMEC/VI was $21,189 per QALY compared with FF/VI and $17,022 per QALY compared with UMEC/VI. For comparison with TIO + SAL/FP 250 mcg/50 mcg, the ICUR for FF/UMEC/VI was $137,990 but FF/UMEC/V was dominant (i.e., lower total costs, greater QALYs) when compared with TIO+SAL/FP 500 mcg/50 mcg. Of note, all ICURs for comparisons with TIO + SAL/FP were unstable and associated with substantial uncertainty. CADTH re-analyses could not address a number of potentially significant limitations of the submission.

CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

July 18, 2018 Meeting

Regrets:

None

Conflicts of Interest:

None