Canadian Agency for Drugs and Technologies in Health

COMMON DRUG REVIEW

CDEC FINAL RECOMMENDATION

UMECLIDINIUM BROMIDE/VILANTEROL TRIFENATATE
(Anoro Ellipta — GlaxoSmithKline Inc.)
Indication: Chronic Obstructive Pulmonary Disease

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that umeclidinium bromide/vilanterol trifenatate (UMEC/VI) be listed for the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, 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] or long-acting anticholinergic [LAAC]).

Reasons for the Recommendation:
1. Randomized controlled trials (RCTs) demonstrated that treatment with UMEC/VI provided statistically significant improvements in trough forced expiratory volume in one second (FEV_1) compared with placebo (studies 373 [N = 1,536] and 418 [N = 308]) and compared with tiotropium (TIO) (studies 360 [N = 846] and 115 [N = 905]).
2. At the submitted price ($[redacted] per 30 doses; $[redacted] per dose), UMEC/VI costs less than indacaterol maleate/glycopyrronium bromide ($87.24 per 30 doses; $2.91 per dose, including wholesaler mark-up as this product was not listed by any CADTH Common Drug Review (CDR)-participating drug plans at the time of the UMEC/VI review), the other LABA/LAAC combination product available in Canada.

Background:
UMEC/VI is a combination of a long-acting muscarinic antagonist and a long-acting beta 2-agonist (LAMA/LABA) indicated for long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema. It is not indicated for the relief of acute deterioration of COPD or for treatment of asthma. UMEC/VI is available as dry powder for oral inhalation (62.5 mcg umeclidinium and 25 mcg vilanterol per oral inhalation) using the Ellipta device. The recommended dose of UMEC/VI is 62.5/25 mcg once daily.

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Summary of CDEC Considerations:
CDEC considered the following information prepared by the CDR: a systematic review of RCTs of UMEC/VI, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues that are important to individuals with COPD.

Patient Input Information
The following is a summary of key information provided by three patient groups in response to the CDR call for patient input:

- COPD patients suffer from difficulty breathing, coughing, fatigue, low energy, wheezing, and exacerbations. Their everyday life is suboptimal and affected by the progressive deterioration of their ability to breathe, talk, sleep, work, and socialize.
- Exacerbations are a source of concern for COPD patients because they are associated with both short- and long-term consequences for their overall health.
- In addition to the medical concerns, patients often feel socially isolated and may suffer social stigma, feel a loss of independence, and develop strained relationships with loved ones, leading to reduced emotional well-being and depression.
- Caregivers also often experience the negative impact of COPD with a toll on their time and energy for managing their own health; it causes fatigue, feelings of isolation, anxiety, and depression.
- There is an unmet need for treatments that can improve lung function and quality of life while reducing exacerbations, fatigue, and hospital admissions, particularly therapies that are convenient and will delay disease progression and improve long-term survival.

Clinical Trials
The CDR systematic review included six phase 3, multi-centre, double-blind RCTs in which once-daily UMEC/VI 62.5/25 mcg was compared with one or both of its individual components (UMEC 62.5 mcg or VI 25 mcg), and with either placebo or TIO 18 mcg, all with once-daily dosage. Participants were adults aged at least 40 years and with moderate to severe COPD. Where it was used, TIO was administered via the HandiHaler device, while all the other treatments were administered using the Ellipta device.

- DB2113373 (study 373, N = 1,536) compared UMEC/VI, UMEC, VI, and placebo over a 24-week period
- DB2113360 (study 360, N = 846), DB2113374 (study 374, N = 872), and ZEP117115 (study 115, N = 905) compared UMEC/VI with TIO over a 24-week period
- DB2114417 (study 417, N = 349) and DB2114418 (study 418, N = 308) compared UMEC/VI, UMEC, VI, and placebo over two 12-week treatment periods that were separated by a 14-day washout period.

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

- COPD exacerbation — defined as an acute worsening of symptoms of COPD requiring the use of any treatment beyond the study drug or rescue salbutamol (i.e., antibiotics, systemic corticosteroids, and/or emergency treatment or hospitalization). Patients who experienced an exacerbation were to be withdrawn from the studies.
- Trough FEV_1 — defined as the mean of FEV_1 measurements obtained 23 and 24 hours after dosing.

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- St. George's Respiratory Questionnaire (SGRQ) — a 50-item questionnaire designed to measure the impact of respiratory disease and its treatment on the patients' health-related quality of life. It consists of 50 items and was specifically developed for patients with chronic airflow limitation. The questionnaire is divided into three dimensions: symptoms (eight items measuring the distress due to respiratory symptoms), activity (16 items measuring the effect of disturbances on mobility and physical activity), and impacts (26 items measuring the psychosocial impact of the disease). Total SGRQ scores range from 0 to 100, where 0 indicates no impairment and 100 indicates worst possible health. The minimal clinically important difference (MCID) for total SGRQ is typically considered to be a change of 4.0 units from baseline.
- EuroQol 5-Dimensions (EQ-5D) — a standardized, self-administered, non–disease-specific instrument for describing and valuing health states, which can be used across all disease areas and states of health. The EQ-5D scale ranges from –1 (worst possible health) to 1 (best possible health) with estimated MCID ranges of 0.03 to 0.08.
- Transition Dyspnea Index (TDI) focal score — an interviewer-administered instrument used to measure change from the baseline in the severity of breathlessness in patients. The scores evaluate ratings for three different categories: functional impairment, magnitude of task, and magnitude of effort. These domains are rated by seven grades, ranging from –3 (major deterioration) to +3 (major improvement). The ratings for each of the three categories are added to form a total TDI score ranging from –9 to +9. Lower TDI score indicates more deterioration in severity of dyspnea, and the MCID is considered to be one unit.
- Exercise endurance time (EET) — determined using endurance shuttle walking test.

The primary efficacy outcome was trough FEV_1 at week 24 in the parallel-group studies (i.e., studies 373, 360, 374, and 115). Trough FEV_1 and EET were the co-primary end points of the crossover studies (i.e., studies 417 and 418).

Efficacy

- UMEC/VI demonstrated greater improvement in trough FEV_1 compared with placebo (studies 373, 417, and 418) and compared with TIO (studies 360, 115, and 374). The least-squares mean differences (LSMDs) between groups were reported as follows:
  - UMEC/VI versus placebo: 0.167 L (95% confidence interval [CI], 0.128 to 0.207) in study 373; 0.211 L (95% CI, 0.172 to 0.249) in study 417; and 0.243 L (95% CI, 0.202 to 0.284) in study 418
  - UMEC/VI versus TIO: 0.090 L (95% CI, 0.039 to 0.141) in study 360; 0.112 L (95% CI, 0.081 to 0.144) in study 115; and 0.060 L (95% CI, 0.010 to 0.109) in study 374.
- UMEC/VI demonstrated statistically significantly greater improvements in SGRQ compared with placebo in study 373 ($P < 0.001$) and compared with TIO in study 115 ($P = 0.006$). There was no statistically significant difference between UMEC/VI and TIO in studies 374 and 360. The LSMDs between groups were reported as follows:
  - UMEC/VI versus placebo: –5.51 (95% CI, –7.88 to –3.13) in study 373
  - UMEC/VI versus TIO: –2.10 (95% CI, –3.61 to –0.59) in study 115 and 0.75 (95% CI, –2.12 to 3.63) in study 360.
- TDI scores were statistically significantly greater with UMEC/VI compared with placebo in study 373 and there was no statistically significant difference between UMEC/VI and TIO in studies 360 and 374. The LSMDs between groups were reported as follows:
  - UMEC/VI versus placebo: 1.2 (95% CI, 0.7 to 1.7) in study 373

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  - UMEC/VI versus TIO: –0.1 (95% CI, –0.7 to 0.5) in study 360 and 0.2 (95% CI, –0.5 to 0.9) in study 374.
- The improvement in three-hour post-dose EET at week 12 was statistically significantly greater with UMEC/VI compared with placebo in study 418 (LSMD 69.4 [95% CI, 24.5 to 114.4], *P* = 0.003), but not in study 417 (LSMD 21.9 [95% CI, –14.2 to 58.0], *P* = 0.234). There were no statistically significant differences between UMEC/VI and any of its individual components in studies 417 or 418.
- In study 418, UMEC/VI demonstrated statistically significant greater improvement in dyspnea at week 12 compared with placebo, as measured by the exercise dyspnea scale (LSMD –0.36 [95% CI, –0.67 to –0.05]; *P* = 0.025); however, there was no statistically significant difference in study 417 (LSMD –0.05 [95% CI, –0.37 to 0.27]; *P* = 0.758).
- There was no statistically significant difference in EQ-5D scores between UMEC/VI and TIO in studies 360 and 374.

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one adverse event was:
  - UMEC/VI (23% to 51%) versus placebo (27% to 46%)
  - UMEC/VI (44% to 51%) versus TIO (39% to 59%).
- Nasopharyngitis and headache were the most commonly reported adverse events.
- The proportion of patients who experienced at least one serious adverse event was:
  - UMEC/VI (2% to 5%) versus placebo (3% to 4%)
  - UMEC/VI (3% to 10%) versus TIO (4% to 6%).
- COPD and related sequelae were the most frequently reported serious adverse events (ranging from < 1% to 3% across all studies).
- The proportion of patients who withdrew from the studies due to adverse events was:
  - UMEC/VI (4% to 5%) versus placebo (3% to 5%)
  - UMEC/VI (4% to 9%) versus TIO (3% to 5%).
- COPD was the most commonly cited adverse event leading to discontinuation in the majority of the included studies.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing UMEC/VI with TIO in adult patients with moderate to severe COPD, $FEV_1 \leq 70\%$ predicted post-bronchodilator, over a 20-year time horizon from the perspective of the public payer. The pharmacoeconomic submission was based on COPD disease progression risk equations that correlate patient characteristics (e.g., age, gender, body mass index, comorbidities, prior exacerbation history, lung function, and exercise capacity), per cent predicted FEV_1, and intermediate outcomes (exacerbations, cough and sputum, and six-minute walk test) to final outcomes (costs, mortality, and quality of life). The risk equations were derived from analyses using data from the observational ECLIPSE study. Data on relative effectiveness between treatments were captured in terms of trough FEV_1 from an unpublished meta-analysis from studies 374, 360, and 115. In the reference case, the manufacturer reported that over a 20-year time horizon, UMEC/VI is associated with cost savings of $153 and a gain of 0.01 QALYs compared with TIO.

CDR identified the follow key limitations with the manufacturer's economic evaluation:

- TIO monotherapy is not considered to be the most relevant comparator to dual LABA/LAMA therapy. The clinical and cost-effectiveness of UMEC/VI compared with that of existing LABA/LAMA combination therapies is unknown.

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- There are inconsistent results in the clinical trials of UMEC/VI versus TIO monotherapy in terms of quality of life measures and FEV_1, which was statistically superior but uncertain clinical significance. This contributes to the uncertainty regarding the clinical benefits and resulting cost-effectiveness of UMEC/VI, as FEV_1 is the only parameter that differentiates UMEC/VI from TIO.
- No statistically significant difference was observed in the studies between UMEC/VI and TIO in dyspnea or improved quality of life, or important patient-related outcomes (e.g., reduced breathlessness) in studies 360 and 374. Therefore, the clinical benefit predicted in the model, although marginal (incremental 0.014 QALYs, or five quality-adjusted days over 20 years) is uncertain and is not supported by the clinical evidence.
- Information on COPD exacerbations was not captured in the RCTs that compared UMEC/VI with TIO.
- Uncertainty exists as to whether FEV_1, as a surrogate outcome, and exacerbations and dyspnea are reliably associated. Further, where this association is established, whether the manufacturer's risk equation captures the association correctly needs to be verified. The association between FEV_1 and exacerbations and dyspnea has not been confirmed in the UMEC/VI clinical studies.
- Applying the correlations derived using the ECLIPSE and TORCH studies might not be appropriate, as these studies included patients on a LABA/ICS regimen, which is used for patients with more severe COPD who are experiencing exacerbations.

Based on the clinical trials for UMEC/VI, the results in terms of clinical outcomes for FEV_1 appear to be inconsistent when compared with TIO. This leads to uncertainty in the manufacturer's pharmacoeconomic model in terms of clinical benefit for UMEC/VI when FEV_1 is used to predict exacerbations and dyspnea.

UMEC/VI ($[redacted] per 30-dose package, or $[redacted] daily) [redacted] TIO ($2.17 per 18 mcg capsule or daily), and less than indacaterol/glycopyrronium ($87.24 per 30 doses; $2.91 per dose, including wholesaler mark-up as this product was not listed by any CDR-participating drug plans at the time of the UMEC/VI review).

Other Discussion Points:
CDEC noted the following:
- Clinical practice guidelines for the management of COPD typically recommend that a patient begin with monotherapy and, if symptoms are inadequately controlled, treatment should be intensified with the addition of a second drug. Although UMEC has received a Notice of Compliance from Health Canada, the individual components of UMEC/VI are not currently marketed in Canada; therefore, patients would not be able to begin monotherapy with UMEC or VI.

Research Gaps:
- The included studies were not designed or powered to assess treatment differences in mortality and morbidity.
- COPD is a chronic condition and all of the included RCTs were short-term studies.
- The included studies did not address the potential use of UMEC/VI as part of a triple therapy regimen in combination with an ICS.
- There are no direct comparative trials with other LABA/LAMA combinations (e.g., indacaterol/glycopyrronium).

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December 10, 2014 Meeting

Regrets:

None

Conflicts of Interest:

None

About This Document:

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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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