CDEC FINAL RECOMMENDATION

UMECLIDINIUM BROMIDE
(Incruse Ellipta — GlaxoSmithKline Inc.)
Indication: Chronic Obstructive Pulmonary Disease

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that umeclidinium 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 conditions are met:

Conditions:
- List in a manner similar to other long-acting muscarinic antagonist (LAMA) monotherapies used in the treatment of COPD
- Limited to monotherapy (i.e., a fixed-dose combination [FDC] long-acting beta-antagonist [LABA]/LAMA should be used if combination therapy is required)
- The drug plan cost for umeclidinium should not exceed the drug plan cost of other LAMA products used as monotherapy for COPD.

Reasons for the Recommendation:
1. Four randomized controlled trials (RCTs) (AC4115408 [N = 206], DB2113373 [N = 1,536], DB2114417 [N = 349]), and DB2114418 [N = 308]) demonstrated that treatment with umeclidinium 62.5 mcg was superior to placebo for improving lung function in patients with moderate to severe COPD. Two RCTs evaluated changes in health-related quality of life (AC4115408 and DB2113373) and both demonstrated that umeclidinium was superior to placebo.
2. At the submitted price ($[redacted] per 30 doses), the daily cost of umeclidinium ($[redacted] per day) is less than the daily cost of all other available LAMAs, based on current list prices (range: $1.77 to $2.17 per day).
3. For patients requiring LAMA and LABA therapy, currently available LABA/LAMA FDCs are less costly than all combinations of umeclidinium plus a LABA.

Background:
Umeclidinium is a LAMA indicated for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema. It is available as a dry powder for oral inhalation using the Ellipta device. The Health Canada–approved dose is 62.5 mcg once daily.

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

Patient Input Information
The following is a summary of key information provided by two patient groups, consisting of patients and caregivers who responded to the CDR call for patient input:

- Patients indicated that COPD affects almost all aspects of daily living, including physical and leisure activities, as well as relationships with family and friends. The most common symptoms are fatigue and shortness of breath, followed by mucus, wheezing, frequent chest infections, and coughing. Inability to perform daily activities results in depression, hopelessness, frustration, and a loss of self-worth.
- 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.
- Patients reported that current treatments provide some relief for COPD symptoms, but their effectiveness diminishes over time. A variety of significant 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 which offer a convenient treatment option for COPD patients who require long-term maintenance therapy are desirable.

Clinical Trials
The CDR systematic review included six double-blind RCTs (AC4115408 [N = 206], DB2113373 [N = 1,536], DB2114417 [N = 349], DB2114418 [N = 308], DB2116132 [N = 207], and DB2116133 [N = 182]). However, studies DB2116132 and DB2116133 were subsequently excluded due to a number of methodological limitations (i.e., primary outcome selection, statistical testing hierarchy, and the prioritization of treatment comparisons). The included studies enrolled patients who were at least 40 years of age and had moderate to severe COPD.

- Study AC4115408 was a 12-week parallel RCT comparing umeclidinium 62.5 mcg, umeclidinium 125 mcg, and placebo.
- Study DB2113373 was a 24-week parallel RCT comparing umeclidinium 62.5 mcg, umeclidinium/vilanterol 62.5 mcg/25 mcg, vilanterol 25 mcg, and placebo.
- Studies DB2114417 and DB2114418 were two-period crossover RCTs comparing umeclidinium 62.5 mcg, umeclidinium/vilanterol 62.5 mcg/25 mcg, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, and placebo.

Data for the umeclidinium 125 mcg once daily, vilanterol 25 mcg once daily, and umeclidinium/vilanterol 125 mcg/25 mcg treatment groups were not included in the CDR review or CDEC deliberations, as these doses are not approved by Health Canada. Data for the umeclidinium/vilanterol 62.5 mcg/25 mcg treatment groups were not included in the CDR review; however, these data were reviewed in the previous CDR review of Anoro Ellipta.

Outcomes

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

- All-cause and COPD-related mortality.
- Health care resource utilization — defined as any contact made with a health care provider about the patient's lung condition that was not related to participation in the study.
- COPD exacerbations — defined as an acute worsening of COPD symptoms requiring the use of antibiotics, systemic corticosteroids, emergency treatment, or hospitalization (treatment beyond study drug or rescue salbutamol).
- Trough forced expiratory volume in one second (trough FEV_1) — defined as the volume of air after a full inspiration that can be forcibly expired in one second. The measure was calculated based on the three highest spirometry measures (from a maximum of eight measures) taken at 23 and 24 hours post-dose. Higher scores are indicative of higher functioning and the minimal clinically important difference (MCID) ranges from 0.10 L to 0.14 L or a 5% to 10% change from baseline.
- Exercise endurance time (EET) — a measure of exercise endurance, and was assessed as the length of time that a patient spends performing the endurance shuttle walk test (ESWT). The ESWT is a standardized, constant-paced field test for the assessment of endurance capacity where patients are instructed to walk for as long as possible (up to a maximum of 20 minutes). The EET was measured three hours after the last scheduled dose administered (12 weeks). Higher scores are indicative of better exercise endurance, and the suggested MCID is a within-patient change of 65 or 70 seconds.
- 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 scores indicate more deterioration in the severity of dyspnea, and the MCID is considered to be one unit.
- St. George's Respiratory Questionnaire (SGRQ) — a self-administered 50-item instrument used to assess impaired health and perceived well-being in respiratory disease. The SGRQ is divided into three dimensions: Symptoms, Activity, and Impacts. Total SGRQ scores range from 0 to 100, with higher values indicating lower health-related quality of life. The MCID has been reported to be an improvement of at least 4 units in the SGRQ total score.
- Rescue salbutamol use — use of rescue medication was defined as the number of puffs used in the previous 24 hours for as-needed relief of the symptoms of COPD.
- Serious adverse events, total adverse events, withdrawals due to adverse events.

The primary efficacy outcome in AC4115408 and DB2113373 was trough FEV_1. There were two co-primary end points (trough FEV_1 and EET) in the exercise endurance studies (DB2114417 and DB2114418).

Efficacy

- There was a statistically significant greater mean change from baseline to end of treatment in trough FEV_1 for the umeclidinium 62.5 mcg group compared with placebo in the 12- and 24-week parallel-group studies and the exercise endurance studies. The change from baseline to end of treatment was clinically significant (least squares [LS] mean change > 0.1 L) in three of the four trials (AC4115408, DB2113373, and DB2114418). The LS mean changes from baseline for umeclidinium 62.5 mcg versus placebo were:
  - Study AC4115408: 0.13 L (95% confidence interval [CI], 0.05 to 0.20)
  - Study DB2113373: 0.12 L (95% CI, 0.08 to 0.16)
  - Study DB2114417: 0.09 L (95% CI, 0.03 to 0.14)
  - Study DB2114418: 0.14 L (95% CI, 0.09 to 0.20).
- There were no statistically significant differences between the umeclidinium 62.5 mcg groups and placebo groups in three hour post-dose EET at week 12 in either exercise endurance study. The LS mean changes from baseline for umeclidinium 62.5 mcg versus placebo were:
  - Study DB2114417: 26.5 seconds (95% CI, −25.9 to 78.9)
  - Study DB2114418: 25.0 seconds (95% CI, −41.0 to 91.0).
- The adjusted mean TDI score for umeclidinium 62.5 mcg versus placebo was not statistically significant in the 12-week study but was statistically significant in the 24-week study. The LS mean changes from baseline for umeclidinium 62.5 mcg versus placebo were:
  - Study AC4115408: 1.0 (95% CI, 0.0 to 2.0)
  - Study DB2113373: 1.0 (95% CI, 0.5 to 1.5).
- There was a statistically and clinically significant improvement in the SGRQ total score for the umeclidinium 62.5 mcg versus placebo in the parallel-group studies:
  - Study AC4115408: −7.9 (95% CI, −12.2 to −3.6)
  - Study DB2113373: −4.7 (95% CI, −7.1 to −2.3).

Harms (Safety and Tolerability)

- The most common AEs across all trials were headache and nasopharyngitis. The percentages of patients experiencing at least one adverse event in the parallel-group studies (AC4115408 and DB2113373) were generally similar between the placebo and umeclidinium 62.5 mcg groups. However, the percentage of patients experiencing adverse events was numerically higher in the placebo group compared with the umeclidinium 62.5 mcg group in the exercise endurance studies.
  - Study AC4115408: umeclidinium 62.5 mcg 39% versus placebo 35%
  - Study DB2113373: umeclidinium 62.5 mcg 52% versus placebo 46%
  - Study DB2114417: umeclidinium 62.5 mcg 12% versus placebo 27%
  - Study DB2114418: umeclidinium 62.5 mcg 30% versus placebo 39%.
- The percentage of patients experiencing at least one serious adverse event was similar between placebo and umeclidinium 62.5 mcg groups in studies AC4115408 and DB2114418. The percentage of patients experiencing a serious adverse event was higher for the umeclidinium 62.5 mcg group compared with placebo in study DB2113373 and lower in the umeclidinium 62.5 mcg group compared with placebo for study DB2114417.
  - Study AC4115408: umeclidinium 62.5 mcg 1% versus placebo 1%
  - Study DB2113373: umeclidinium 62.5 mcg 6% versus placebo 3%
  - Study DB2114417: umeclidinium 62.5 mcg 0% versus placebo 4%

  - Study DB2114418: umeclidinium 62.5 mcg 3% versus placebo 3%.
- The proportions of patients who withdrew as a result of adverse events were:
  - Study AC4115408: umeclidinium 62.5 mcg 1% versus placebo 0%
  - Study DB2113373: umeclidinium 62.5 mcg 8% versus placebo 3%
  - Study DB2114417: umeclidinium 62.5 mcg 4% versus placebo 5%
  - Study DB2114418: umeclidinium 62.5 mcg 3% versus placebo 5%.
- Dry mouth and voice hoarseness from current bronchodilators and the adverse effects that manifest themselves following the management of acute exacerbation with prednisone or antibiotics was a concern expressed by patient groups. No cases of voice hoarseness were reported and < 1% of patients across treatment groups in the included studies experienced dry mouth.

Cost and Cost-Effectiveness

The manufacturer submitted a cost comparison of umeclidinium with other LAMA monotherapies used in the treatment of COPD: tiotropium 18 mcg once daily, glycopyrronium bromide 50 mcg once daily, and aclidinium bromide 400 mcg twice daily. The analysis was undertaken from the public-payer perspective. Prices from the Ontario Drug Benefit formulary (November 2014) were used to calculate the cost of comparator drugs. The assumption of similar treatment efficacy was based on a manufacturer-sponsored indirect treatment comparison (ITC), where umeclidinium and all other comparators were found to be similar in clinical efficacy in terms of lung function (assessed by trough FEV_1 at 12 weeks) and for other clinical outcomes (trough FEV_1 at 24 weeks, SGRQ score, TDI score, and the use of rescue medication).

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

- Exacerbations and exercise tolerance were not considered in the manufacturer's ITC.
- Due to limitations in the ITC, there is some uncertainty regarding the comparative effectiveness of umeclidinium versus other LAMAs for the outcomes considered.
- Lack of consideration of LABA monotherapy and inhaled corticosteroid (ICS)/LABA combinations, both of which are appropriate comparators.

At the submitted price ($[redacted] per 30 doses; $[redacted] per day), umeclidinium is less costly than the current list price of all other available LAMAs ($1.77 daily, aclidinium or glycopyrronium; $2.17 daily, tiotropium). Umeclidinium is more costly than most monotherapy LABA products (range: $1.55 to $1.87 daily). For patients requiring LAMA and LABA therapy, currently available LAMA/LABA FDCs are less costly than all possible combinations of umeclidinium plus a LABA.

Other Discussion Points:

CDEC noted the following:

- Umeclidinium was previously reviewed as part of Anoro Ellipta (an FDC consisting of umeclidinium/vilanterol) and received a recommendation to list with clinical criteria.
- CDEC noted that there is a risk of dose escalation with pharmacotherapies for COPD. There is no evidence to suggest that increasing the dosage of umeclidinium to a level above the dose recommended in the product monograph (i.e., 62.5 mcg per day) would be associated with increased clinical benefits for patients. In addition, increasing the dosage would result in greater costs for the CDR-participating drug plans.

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

- There were no studies directly comparing umeclidinium against other long-acting monotherapy treatments for COPD.
- There was no comparative evidence available to assess the safety of umeclidinium versus other long-acting monotherapy treatments.
- The included studies were not designed or powered to assess treatment differences in mortality and morbidity.

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.

August 19, 2015 Meeting

Regrets:
None

Conflicts of Interest:
One CDEC member did not participate in the 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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