CDEC FINAL RECOMMENDATION

ACLIDINIUM/FORMOTEROL
(Duaklir Genuair — AstraZeneca Canada Inc.)
Indication: Chronic Obstructive Pulmonary Disease

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that aclidinium bromide/formoterol fixed-dose combination (FDC) be listed for long-term maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, if the following conditions are met:

Conditions:
- List in a manner similar to other long-acting muscarinic antagonist (LAMA)/long-acting beta-agonist (LABA) FDC products.
- Drug plan costs for aclidinium/formoterol should not exceed drug plan costs for other listed LAMA/LABA combination products.

Reasons for Recommendation:
1. Two pivotal randomized controlled trials (RCTs) (LAC 30 [N = 1,726] and LAC 31 [N = 1,668]) demonstrated that treatment with aclidinium/formoterol was superior to placebo for improving FEV_1, dyspnea, and health-related quality of life.
2. One RCT (LAC 39 [N = 933]) demonstrated that aclidinium/formoterol was superior to salmeterol/fluticasone for improving peak FEV_1 and similar to salmeterol/fluticasone for improving trough FEV_1, dyspnea, and health-related quality of life.
3. At the submitted price ($74.10 per 60 actuations; $2.47 per day), aclidinium/formoterol is less costly than other LAMA/LABA FDCs ($2.67 to $2.70 per day) and separately administered combinations of individual LAMA + LABA products ($3.26 to $3.85 per day).

Background:
Aclidinium/formoterol FDC contains the LAMA aclidinium bromide (400 mcg) and the LABA formoterol fumarate dihydrate (12 mcg), delivered via the Genuair multi-dose dry powder inhaler (mDPI). It is indicated as a long-term, twice-daily maintenance bronchodilator treatment for airflow obstruction in patients with COPD including chronic bronchitis and/or emphysema. The recommended dose is one inhalation twice daily.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a review of manufacturer-provided information on the therapeutic rationale, place in therapy, bioequivalence, efficacy, and harms for the combined use of aclidinium and formoterol; a critique of the manufacturer's pharmacoeconomic evaluation; and patient group–submitted information about outcomes and issues that are important to individuals living with COPD.

Patient Input Information
The following is a summary of key information provided by two patient groups consisting of patients and caregivers that 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 review included five multinational, double-blind RCTs. All studies enrolled patients who were at least 40 years of age, had a diagnosis of stable moderate to severe COPD, and had a history of smoking (at least 10 pack-years). Two studies (LAC 30 [N = 1,726] and LAC 31 [N = 1,668]) were pivotal trials that compared aclidinium/formoterol FDC with placebo, aclidinium monotherapy, and formoterol monotherapy. Study LAC 36 was a 28-week extension study of LAC 31 for patients from the United States and Canada (N = 716). Study LAC 39 (N = 933) was a non-inferiority study that compared aclidinium/formoterol FDC with salmeterol/fluticasone. Study LAC 32 (N = 590) was designed to assess the long-term safety and tolerability of aclidinium/formoterol FDC versus formoterol monotherapy.

Outcomes
CDEC discussed the following outcomes:

- COPD exacerbations — defined as an increased symptom or new onset of two or more of the following for a duration of three days or more and requiring a change in treatment: shortness of breath or dyspnea, shallow, rapid breathing, sputum production, occurrence of purulent sputum, cough, wheezing, and chest tightness. A change in or requirement of treatment included the prescription of antibiotics and/or systemic corticosteroids and/or a significant change of the prescribed respiratory medication.

- FEV_1 — including trough FEV_1 measured 24 hours post-drug administration on the last day of treatment, peak FEV_1, and FEV_1 one hour 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.
- 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 four units in the SGRQ total score.

There were two co-primary outcomes in LAC 30 and LAC 31: change from baseline to week 24 in FEV_1 at one hour post-dose for aclidinium/formoterol FDC versus aclidinium; and change from baseline to week 24 in morning trough FEV_1 for aclidinium/formoterol FDC versus formoterol. The primary outcome of LAC 39 was change from baseline in peak FEV_1 at week 24 for aclidinium/formoterol FDC with salmeterol/fluticasone. Primary outcomes were not specified for LAC 32 and LAC 36, as these were primarily safety studies.

Efficacy

Pivotal studies (LAC 30 and LAC 31)

- There were no statistically significant differences in COPD exacerbations between aclidinium/formoterol and aclidinium, formoterol, or placebo at 24 weeks in the individual studies. However, a pooled analysis demonstrated statistically significantly fewer moderate to severe COPD exacerbations with aclidinium/formoterol versus placebo at 24 weeks. The rate ratios for moderate to severe COPD exacerbations with aclidinium/formoterol versus placebo were:
  - LAC 30: 0.77 (95% confidence interval [CI], 0.44 to 1.36); $P = 0.37$
  - LAC 31: 0.69 (95% CI, 0.46 to 1.02); $P = 0.066$
  - Pooled: 0.71 (95% CI, 0.51 to 0.98); $P = 0.036$.
- For improvement in FEV_1 at one hour post-dose, aclidinium/formoterol was statistically superior to placebo, aclidinium alone, and formoterol alone (all $P < 0.0001$). The least-squares mean differences (LSMDs) were:
  - Aclidinium/formoterol versus placebo: 0.299 L (95% CI, 0.255 to 0.343) in LAC 30 and 0.284 L (95% CI, 0.247 to 0.320) in LAC 31
  - Aclidinium/formoterol versus formoterol: 0.139 L (95% CI, 0.104 to 0.174) in LAC 30 and 0.0825 L (95% CI, 0.047 to 0.118) in LAC 31
  - Aclidinium/formoterol versus aclidinium: 0.125 L (95% CI, 0.090 to 0.160) in LAC 30 and 0.108 L (95% CI, 0.073 to 0.144) in LAC 31.

- For improving trough FEV_1, aclidinium/formoterol was statistically superior to placebo and formoterol alone, but not aclidinium alone. The LSMDs were:
  - Aclidinium/formoterol versus placebo: 0.143 (95% CI, 0.101 to 0.185) in LAC 30 and 0.130 (95% CI, 0.095 to 0.165) in LAC 31
  - Aclidinium/formoterol versus formoterol: 0.085 (95% CI, 0.051 to 0.119) in LAC 30 and 0.0448 (95% CI, 0.011 to 0.079) in LAC 31
  - Aclidinium/formoterol versus aclidinium: 0.026 (95% CI, −0.007 to 0.060) in LAC 30 and 0.028 (95% CI, −0.006 to 0.063) in LAC 31.
- For dyspnea, aclidinium/formoterol was statistically superior to placebo for improving TDI scores; however, there were no statistically significant differences between aclidinium/formoterol and aclidinium or formoterol alone. The LSMDs were:
  - Aclidinium/formoterol versus placebo: 1.29 (95% CI, 0.73 to 1.86) in LAC 30 and 1.44 (95% CI, 0.85 to 2.02) in LAC 31
  - Aclidinium/formoterol versus formoterol: 0.45 (95% CI, −0.00 to 0.90) in LAC 30 and 0.49 (95% CI, −0.07 to 1.06) in LAC 31
  - Aclidinium/formoterol versus aclidinium: 0.40 (95% CI, −0.05 to 0.85) in LAC 30 and 0.46 (95% CI, −0.10 to 1.02) in LAC 31.
- Aclidinium/formoterol was superior to placebo for improving SGRQ total score in LAC 31 (LSMD: –4.35; 95% CI, –6.64 to –2.24), but not in LAC 30 (LSMD: –0.65 L; 95% CI, –3.08 to 1.78). There were no statistically significant differences between aclidinium/formoterol and the individual components in either study.

Non-inferiority study (LAC 39)

- Aclidinium/formoterol was non-inferior and superior to salmeterol/fluticasone for change from baseline in peak FEV_1, with the following LSMDs:
  - Non-inferiority analysis: 0.101 L (95% CI, 0.070 to 0.131); $P < 0.0001$
  - Superiority analysis: 0.093 L (95% CI, 0.063 to 0.123); $P < 0.001$.
- There was no statistically significant difference between aclidinium/formoterol and salmeterol/fluticasone for change from baseline in trough FEV_1 (LSMD: −0.014 L; 95% CI, –0.043 to 0.016).
- There was no statistically significant difference between aclidinium/formoterol and salmeterol/fluticasone for change from baseline in TDI score (LSMD: 0.0; 95% CI, −0.46 to 0.46) or SGRQ (LSMD: 1.0; 95% CI, −0.80 to 2.86).

Longer-term study (LAC 32)

- At 52 weeks, a statistically significantly greater improvement from baseline for trough FEV_1 was observed with aclidinium/formoterol compared with formoterol (LSMD: 0.082 L; 95% CI, 0.01 to 0.15 L; $P = 0.02$).
- There was no statistically significant difference in the rate of moderate to severe COPD exacerbations between aclidinium/formoterol and formoterol alone (0.52 per patientyear and 0.49 per patient-year, respectively).

Extension study (LAC 36)

- Over the 52-week treatment period, adjusted mean differences in one hour post-dose FEV_1 between aclidinium/formoterol and placebo ranged from 0.284 L to 0.299 L ($P < 0.0001$).

Statistically significant improvements were observed at all time-points up to week 52 with aclidinium/formoterol relative to formoterol or aclidinium alone.

- Adjusted mean differences in trough FEV_1 between aclidinium/formoterol and placebo ranged from 0.118 L to 0.152 L ($P < 0.0001$). At week 52, there was no statistically significant difference between aclidinium/formoterol and aclidinium alone for change from baseline in trough FEV_1 ($P = 0.7211$).
- Aclidinium/formoterol was associated with statistically significant improvements in TDI scores compared with placebo over the 52-week treatment period (mean differences ranged from 1.07 to 1.49); however, there was no statistically significant difference between aclidinium/formoterol and formoterol or aclidinium alone.

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one serious adverse event in the pivotal studies was placebo (7.4%), aclidinium/formoterol (8.1%), aclidinium (7.3%), and formoterol (6.8%).
- The proportion of patients who experienced at least one adverse event in the pivotal studies was similar across the treatment groups: placebo (62.2%), aclidinium/formoterol (62.4%), aclidinium (62.6%), and formoterol (65.6%). The most commonly reported adverse events (incidence > 5%) in patients treated with aclidinium/formoterol were exacerbations of COPD, nasopharyngitis and headache.
- The proportion of patients who withdrew from the pivotal studies as a result of adverse events was placebo (8.4%), aclidinium/formoterol (7.2%), aclidinium (6.8%), and formoterol (5.7%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing aclidinium/formoterol with other available LAMA/LABA FDCs (i.e., umeclidinium/vilanterol and indacaterol/glycopyrronium) and LAMA + LABA combinations administered as separate inhalers (i.e., aclidinium + formoterol, glycopyrronium + formoterol, and tiotropium + formoterol). The assumption of similar efficacy and safety was based on a manufacturer-sponsored mixed-treatment comparison (MTC), where aclidinium/formoterol and available LAMA/LABA FDCs were found to be comparable in terms of efficacy on lung function parameters (assessed by change from baseline in trough and peak FEV_1) and other outcomes such as SGRQ score, TDI score, COPD exacerbations, and withdrawals due to adverse events. The efficacy and safety of LAMA + LABA combinations administered as separate inhalers were assumed to be comparable to the FDCs. Costs considered were drug acquisition costs, outpatient pharmacy costs, medical visits, lab and diagnostic procedures, and lung function studies. The analysis was undertaken from the public-payer perspective and used a one-year time horizon.

CDR noted the following limitations of the manufacturer's analysis:

- Questionable relevance of separately administered monotherapies as comparators.
- Uncertainty regarding comparative effectiveness of aclidinium/formoterol versus other LAMA + LABA combinations due to limitations in the MTC.

Given the findings from the manufacturer's MTC, differences in health care resource use are unlikely; therefore, at the submitted price of $2.47 per day, aclidinium/formoterol was considered

less costly than other LAMA/LABA FDCs (range: $2.67 to $2.70 daily) and separately administered LAMA + LABA combinations (range: $3.26 to $3.85 daily).

Other Discussion Points:
CDEC noted the following:

- Aclidinium/formoterol is administered twice daily, whereas other LAMA/LABA combination inhalers (i.e., indacaterol/glycopyrronium and umeclidinium/vilanterol) are administered once daily. Patient groups stated that twice-daily administration can be preferred for those patients with more severe morning symptoms. CDEC noted that the need for twice-daily administration is unlikely to have a negative impact on adherence for patients with COPD.
- 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 aclidinium bromide/formoterol to a level above the dose recommended in the product monograph (i.e., one inhalation twice daily) 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 are no direct comparisons against other LAMA/LABA combination inhalers, such as indacaterol/glycopyrronium FDC and umeclidinium/vilanterol FDC.

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 CDEC 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 not requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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