CDEC FINAL RECOMMENDATION

ACLIDINIUM BROMIDE
(Tudorza Genuair — Almirall Canada Ltd.)
Indication: Chronic Obstructive Pulmonary Disease

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that aclidinium bromide be listed for the treatment of chronic obstructive pulmonary disease (COPD) if the following conditions are met:

Conditions:
- List in a manner similar to other long-acting antimuscarinic antagonists (LAMAs).
- Drug plan costs for aclidinium bromide should not exceed the cost of any other LAMA.

Reasons for the Recommendation:
1. Six double-blind randomized controlled trials (RCTs) demonstrated statistically significant improvements in trough FEV_1 with aclidinium bromide compared with placebo and suggested similar efficacy as compared with tiotropium and formoterol in patients with moderate to severe COPD.

2. At the recommended dose, the daily cost of aclidinium bromide ($[redacted]) is less than the daily cost of tiotropium ($2.17), but more than the cost of glycopyrronium bromide ($1.77).

Background:
Aclidinium bromide is an inhaled LAMA indicated for long-term maintenance bronchodilator treatment in patients with COPD, including chronic bronchitis and emphysema. Aclidinium bromide is available in a pre-loaded, multi-dose dry powder inhaler and the product monograph recommends a dose of 400 mcg twice daily by oral inhalation.

Summary of CDEC Considerations
CDEC considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of aclidinium bromide, 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 two patient groups that responded to the CDR call for patient input:

- Individuals with COPD commonly experience difficulty breathing, as well as coughing, shortness of breath, fatigue, weakness, lack of appetite, and difficulty talking. Performing everyday tasks can be difficult and patients become limited in their ability to participate in social interactions, occupational activities, and leisure activities. The disease has a progressive debilitating course. People with COPD and their caregivers often experience anxiety and depression.
- Currently available treatments provide some symptom relief, but are limited by side effects such as palpitations, dry mouth, voice hoarseness, mouth sores, and visual and urinary problems. Exacerbations are often managed with prednisone, which can have dangerous side effects such as stomach upset, general swelling, and increases in the risk of osteoporosis and ophthalmic disease. There is also a concern that these medications lose effectiveness over time.
- Patient groups state that treatments are needed to improve lung function and breathing.

Clinical Trials

The CDR systematic review included six prospective, double-blind, RCTs. Three were placebo-controlled trials (M/34273/34 [N = 828], LAS-MD-33 [N = 561] and LAS-MD-38A [N = 544]), and three were active comparator trials (M/34273/23 [N = 30], M/34273/29 [N = 79] and M/34273/39 [N = 414]). The placebo-controlled trials ranged from 12 to 24 weeks duration and also included an aclidinium bromide 200 mcg twice daily group; however, as this is not an approved dose, results from this treatment group were not reported in the CDR review. Two of the active comparator trials (M/34273/23 and M/34273/29) were phase II crossover trials with treatment periods of 15 days and seven days, respectively; whereas, M/34273/39 was a phase III parallel group trial of six weeks duration. All of the trials included patients who were at least 40 years of age, had moderate to severe COPD, and had smoked for at least 10 pack-years.

Outcomes

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

- COPD exacerbations — defined as an increase in COPD symptoms for at least two consecutive days with severity categorized as follows:
  - Mild: increase of COPD symptoms during at least two consecutive days, self-managed by the patient at home by increasing usual COPD medication (short-acting bronchodilator or inhaled corticosteroid use).
  - Moderate: increase of COPD symptoms during at least two consecutive days, which does not lead to hospitalization, but is treated with antibiotics and/or systemic corticosteroids, or an increase in dose of systemic corticosteroids.
  - Severe: increase in COPD symptoms during at least two consecutive days, which leads to hospitalization (overnight stay at hospital or emergency room).
- Trough FEV_1 assessed at 12 weeks and 24 weeks using the average of two pre-dose FEV_1 measurements conducted just before to the morning dose of study drug.
- Normalized area under the curve (AUC) for FEV_1 assessed over 12 hours ($AUC_{0\text{-}12/12h}$) or 24 hours ($AUC_{0\text{-}24/24h}$) and was measured on the last day of the study period.

- The Transition Dyspnea Index (TDI) — score is based on three categories (functional impairment, magnitude of task, and magnitude of effort) each scored from –3 to 3, to give an overall score of –9 to 9.
- 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.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The primary efficacy outcome in the three placebo-controlled trials was the change from baseline in trough FEV_1 at 12 weeks (LAS-MD-33, LAS-MD-38A, and M/34273/34 for filing with Health Canada and the US Food and Drug Administration) and 24 weeks (M/34273/34 for filing with the European Medicines Agency). The primary efficacy outcome in the active comparator trials was the normalized FEV_1 $AUC_{0\text{-}12/12\ h}$ (M/34273/23 and M/34273/29) or $AUC_{0\text{-}24/24\ h}$ (M/34273/39) at the end of the study period.

Efficacy

- Aclidinium bromide was superior to placebo for improvements in trough FEV_1 at 6, 12, and 24 weeks. The least square mean differences (LSMDs; 95% CI) for aclidinium bromide versus placebo were reported as follows:
  - 6 weeks: 0.141 L (0.083 to 0.199) in M/34273/39.
  - 12 weeks: 0.105 L (0.065 to 0.144) in M/34273/34, 0.124 L (0.08 to 0.16) in LAS-MD-33, and 0.072 L (0.03 to 0.12) in LAS-MD-38A.
  - 24 weeks: 0.128 L (0.085 to 0.170) in M/34273/34.
- There was no statistically significant differences between aclidinium bromide and tiotropium in trough FEV_1 in M/34273/39 (LSMDs: 0.038 L [95% CI: –0.010 to 0.087]) or M/34273/23 (LSMDs: 0.036 L [95% CI: –0.027 to 0.099]) and no statistically significant difference between aclidinium bromide and formoterol (LSMDs: 0.007 L [95% CI: –0.036 to 0.050]) in M/34273/29.
- Aclidinium bromide was superior to placebo for normalized FEV_1 $AUC_{0\text{-}12}$ at day 1 (LSMDs: 0.149 L [95% CI: 0.105 to 0.192]), normalized FEV_1 $AUC_{0\text{-}24}$ at week 6 (LSMDs: 0.150 L [95% CI: 0.094 to 0.205]), and normalized FEV_1 $AUC_{12\text{-}24}$ at week 6 (LSMDs: 0.160 L [95% CI: 0.103 to 0.217]) in M/34273/39.
- There were no statistically significant differences between aclidinium bromide and tiotropium in M/34273/39 for changes in FEV_1 $AUC_{0\text{-}12}$, FEV_1 $AUC_{0\text{-}24}$, and FEV_1 $AUC_{12\text{-}24}$.
- Aclidinium bromide was superior to placebo for improvements in SGRQ at 4, 12, and 24 weeks in M/34273/34 and LAS-MD-33, but not in LAS-MD-38A. The LSMDs (95% CI) for aclidinium bromide versus placebo were reported as follows:
  - 4 weeks: –2.59 (–4.30 to –0.89) in M/34273/34, –3.6 (–5.4 to –1.8) in LAS-MD-33, –0.6 (–2.7 to 1.5) in LAS-MD-38A.
  - 12 weeks: –4.10 (–6.06 to –2.13) in M/34273/34, –2.5 (–4.7 to –0.4) in LAS-MD-33, –1.1 (–3.8 to 1.6) in LAS-MD-38A.
  - 24 weeks: –4.63 (–6.84 to –2.42) in M/34273/34.
- Aclidinium bromide was superior to placebo for improvements in TDI focal score at 4, 12, and 24 weeks. The LSMDs (95% CI) for aclidinium bromide versus placebo were reported as follows:
  - 4 weeks: 0.92 (0.44 to 1.39) in M/34273/34, 0.9 (0.2 to 1.5) in LAS-MD-33.
  - 12 weeks: 0.88 (0.35 to 1.41) in M/34273/34, 1.0 (0.4 to 1.6) in LAS-MD-33, 1.0 (0.3 to 1.7) in LAS-MD-38A.

  - 24 weeks: 1.00 (0.43 to 1.57) in M/34273/34.
- Hazard ratios (HR) for the time to first COPD exacerbation of any severity for aclidinium bromide versus placebo were 0.64 (95% CI: 0.42 to 0.97) in M/34273/34, 0.7 (95% CI: 0.3 to 1.4) in LAS-MD-33, and 0.8 (95% CI: 0.4 to 1.6) in LAS-MD-38A.

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one adverse event was reported as follows:
  - M/34273/34: aclidinium bromide (53.5%) and placebo (57.1%).
  - LAS-MD-33: aclidinium bromide (44.7%) and placebo (52.2%).
  - LAS-MD-38A: aclidinium bromide (50.8%) and placebo (49.5%).
  - M/34273/23: aclidinium bromide (24.1%), tiotropium (10.7%), and placebo (26.7%).
  - M/34273/29: aclidinium bromide (18.9%), formoterol (14.9%), and placebo (21.1%).
  - M/34273/39: aclidinium bromide (27.5%), tiotropium (29.7%), and placebo (25.9%).
- The proportion of patients who experienced at least one serious adverse event was reported as follows:
  - M/34273/34: aclidinium bromide (5.6%) and placebo (5.5%).
  - LAS-MD-33: aclidinium bromide (3.2%) and placebo (2.2%).
  - LAS-MD-38A: aclidinium bromide (4.5%) and placebo (6.6%).
  - M/34273/23: aclidinium bromide (0%), tiotropium (0%), and placebo (3.3%).
  - M/34273/29: aclidinium bromide (1.4%), formoterol (0%), and placebo (2.6%).
  - M/34273/39: aclidinium bromide (1.8%), tiotropium (2.5%), and placebo (0%).
- The proportion of patients who withdrew due to adverse events was reported as follows:
  - M/34273/34: aclidinium bromide (3.0%) and placebo (4.0%).
  - LAS-MD-33: aclidinium bromide (4.2%) and placebo (7.5%).
  - LAS-MD-38A: aclidinium bromide (7.3%) and placebo (4.4%).
  - M/34273/23: aclidinium bromide (0%), tiotropium (0%), and placebo (10.0%).
  - M/34273/29: aclidinium bromide (2.7%), tiotropium (1.4%), and placebo (4.0%).
  - M/34273/39: aclidinium bromide (1.8%), tiotropium (1.3%), and placebo (2.5%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis in which aclidinium bromide was compared with tiotropium and glycopyrronium bromide. Based on the results of an indirect treatment comparison submitted by the manufacturer, the manufacturer assumed that aclidinium bromide, tiotropium, and glycopyrronium bromide have similar efficacy and harms. The manufacturer assumed that indirect costs were the same for the three drugs, except for the cost of secondary pharmacotherapy. When assuming no difference in secondary pharmacotherapy, recalculations by CDR of the cost of treatments indicated that when compared with tiotropium, aclidinium bromide was associated with annual savings of $[redacted] per patient, but the annual cost of aclidinium bromide was $[redacted] more per patient when compared with glycopyrronium bromide. The submitted price of aclidinium bromide is $[redacted] per inhaler or $[redacted] per day at the recommended dose of 400 mcg twice daily. The cost of tiotropium is $2.17 per day (18 mcg once daily), and the cost of glycopyrronium bromide is $1.77 per day (50 mcg once daily).

Other Discussion Points:
CDEC noted the following:

- Aclidinium bromide is administered twice daily; whereas, tiotropium and glycopyrronium bromide are administered once daily.
- Patients in the included RCTs appeared to have a preference for the Genuair device compared with the HandiHaler or Aerolizer devices. However, caution is warranted in the interpretation of these results, as patient satisfaction within the setting of an RCT may not be reflective of results in routine clinical usage.
- Study LAS-MD-38A had an unequal baseline of COPD severity in patients randomized to aclidinium bromide than placebo. The diminished treatment effect in LAS-MD-38A could be attributable to this failure of randomization.
- The included trials were of insufficient duration to accurately assess the impact of seasonality on the efficacy of aclidinium bromide, an important factor in the management of COPD in Canada.
- Several patient characteristics affect the generalizability of the results of the included trials to Canadian COPD patients, including a younger population with a higher proportion of current smokers than is typically treated for COPD in Canada. The pattern of pre-study COPD medication use was not reflective of what is generally prescribed in Canada (i.e., relatively low usage of long-acting beta2-agonist (LABA) and LABA plus inhaled corticosteroid combinations).

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

- None of the included RCTs were designed or powered to assess treatment differences in COPD exacerbations.
- COPD is a chronic condition and all of the included RCTs were short-term studies.

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.

March 19, 2014 Meeting
Regrets:
None

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

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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