Aclidinium bromide/formoterol fumarate (Duaklir® Pressair®) 
Abbreviated New Drug Update (ANDU)

May 2019

OVERVIEW¹

• Aclidinium bromide/formoterol fumarate (Duaklir Pressair), a combination of an anticholinergic and a long-acting beta₂-adrenergic agonist (LABA), is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). It is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

• Contraindications
  – Use without an inhaled corticosteroid is contraindicated in patients with asthma; aclidinium bromide/formoterol fumarate is not indicated for the treatment of asthma
  – Patients with severe hypersensitivity to milk proteins
  – Patients with a hypersensitivity to any component of the product

• Warnings
  – The use of monotherapy LABA without an inhaled corticosteroid is associated with an increased risk of asthma associated death (class effect).
  – The safety and efficacy of aclidinium bromide/formoterol fumarate has not been established in patients with asthma.
  – Use in patients with acutely deteriorating COPD has not been studied; do not initiate in patients with acutely deteriorating COPD.
  – Should not be used for relief of acute symptoms
  – A rescue medication (e.g., inhaled short-acting beta₂-agonist [SABA]) should be prescribed when treating a patient with aclidinium bromide/formoterol fumarate; discontinue scheduled use of an inhaled SABA
  – Significant cardiovascular adverse reactions and fatalities have been reported related to excessive use of inhaled sympathomimetic medications; do not use more than recommended dosage or in combination with other LABAs.
  – Paradoxical bronchospasm, potentially life-threatening, may occur with inhaled medications, including aclidinium bromide/formoterol fumarate. If a paradoxical bronchospasm occurs, aclidinium bromide/formoterol fumarate should be stopped and an alternative medication should be administered.
If hypersensitivity reactions to aclidinium bromide/formoterol fumarate occur (e.g., anaphylaxis, angioedema, urticaria, rash, bronchospasm, itching), discontinue use.

May cause increases in pulse rate, electrocardiogram (ECG) changes, and systolic or diastolic blood pressure.

Use with caution in patients with convulsive disorders, thyrotoxicosis, and in patients usually responsive to sympathomimetic amines.

May produce hypokalemia and hyperglycemia.

Use with caution in patients with narrow-angle glaucoma, urinary retention, or bladder neck obstruction.

• Drug Interactions
  – Xanthine derivatives, steroids, diuretics, including non-potassium sparing diuretics may cause hypokalemia or ECG changes
  – Monoamine oxidase inhibitors or tricyclic antidepressants may increase effects on the cardiovascular system
  – Beta blockers – only use concomitantly when medically necessary
  – Anticholinergics – avoid concurrent use (additive effect)

• Common Adverse Effects
  – The most common adverse effects (incidence ≥ 3% and more common than placebo) are upper respiratory tract infection, headache, and back pain.

• Special Populations
  – Pregnancy – No adequate, well-controlled studies of aclidinium bromide/formoterol fumarate or its individual components in pregnant women to establish drug-associated risks.
  – Pediatrics – Not indicated for use in children; the safety and efficacy has not been established.

• Availability
  – Breath-activated, multi-dose dry powder for inhalation
  – 400 mcg aclidinium bromide/12 mcg formoterol fumarate per actuation

• Dosage
  – 1 inhalation (400 mcg aclidinium bromide/12 mcg formoterol fumarate) twice daily (morning and evening)

**CLINICAL TRIALS**

• In a 24-week, double-blind, phase 3 study (AUGMENT-COPD; n=1,692), patients with stable COPD were randomized to twice daily aclidinium 400 mcg/formoterol 12 mcg, aclidinium 400 mcg/formoterol 6 mcg, aclidinium 400 mcg, formoterol 12 mcg, or placebo. Coprimary endpoints were the change from baseline to week 24 in 1-hour, morning, postdose predicted forced expiratory volume in 1 second (FEV1) and morning predose FEV1. Secondary endpoints were the change from baseline in the St. George’s Respiratory Questionnaire (SGRQ) total score and improvement in
Transition Dyspnea Index (TDI) focal score. The study resulted with greater improvements in baseline in 1-hour postdose FEV₁ in patients using aclidinium 400 mcg/formoterol 12 mcg or aclidinium 400 mcg/formoterol 6 mcg compared to aclidinium monotherapy (treatment difference, 108 mL and 87 mL, respectively; p<0.0001). At the conclusion of the study, improvements in SGRQ and TDI focal scores were observed in the aclidinium 400 mcg/formoterol 12 mcg (p<0.0001) with differences compared to placebo surpassing the minimal clinically important difference of ≥ 4 points and ≥ 1 unit, respectively.

- A 24-week, double-blind, parallel-group, active- and placebo-controlled, phase 3, multicenter study (ACLIFORM-COPD) was performed. Patients were randomized to aclidinium 400 mcg/formoterol 12 mcg (n=385), aclidinium 400 mcg/formoterol 6 mcg (n=381), aclidinium 400 mcg (n=385), formoterol 12 mcg (n=384), or placebo (n=194) twice daily. At week 24, aclidinium 400 mcg/formoterol 12 mcg and aclidinium 400 mcg/formoterol 6 mcg resulted in significant improvements from baseline in 1-hour postdose FEV₁ versus aclidinium alone (treatment differences of 125 mL [95% confidence interval (CI), 90 to 160; p<0.001] and 69 mL [95% CI: 34, 105; p<0.001], respectively) and trough FEV₁ versus formoterol (treatment differences of 85 mL [95% CI: 51, 119; p<0.001] and 53 mL [95% CI: 19, 87; p<0.01], respectively). There were also improvements in TDI focal score with aclidinium 400 mcg/formoterol 12 mcg and aclidinium 400 mcg/formoterol 6 mcg compared to placebo (1.29 units [95% CI: 0.73, 1.86; p<0.001] and 1.16 units [95% CI: 0.59, 1.73; p<0.001], respectively).

- AMPLIFY was a 24-week, phase 3, double-dummy, active-controlled study in which 1,594 symptomatic patients (COPD Assessment Test score ≥ 10) were randomized to twice-daily aclidinium 400 mcg/formoterol 12 mcg, aclidinium 400 mcg, formoterol 12 mcg, or once daily tiotropium 18 mcg. The endpoints assessed at week 24 were the change from baseline in 1-hour morning postdose FEV₁ (aclidinium/formoterol versus aclidinium) and in pre-dose trough FEV₁ (aclidinium/formoterol versus formoterol). Aclidinium noninferiority to tiotropium in pre-dose FEV₁ and normalized area under the curve (AUC)₀-3/₃h FEV₁ and night-time and early morning symptoms were also assessed. A subgroup of 566 patients participated in a 24-hour serial spirometry study. The 1-hour postdose FEV₁ improved significantly with aclidinium/formoterol versus aclidinium, formoterol, and tiotropium (84 mL, 84 mL, and 92 mL, respectively; p<0.0001). Aclidinium/formoterol significantly improved trough FEV₁ compared to formoterol (55 mL; p<0.001) and aclidinium was noninferior to tiotropium. Aclidinium/formoterol improved AUC₀-3/₃h FEV₁ versus comparators (p<0.0001) and improved early morning symptoms compared to tiotropium. At week 24, the 24-hour spirometry showed larger improvements with aclidinium/formoterol in AUC₁₂-2₄₄/₁₂h versus comparators and in AUC₀-2₄/2₄ h versus formoterol or tiotropium.

**CLINICAL CONSIDERATIONS**⁵,⁶,⁷

- COPD is a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema. The airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible.
• COPD continues to be a leading cause of chronic morbidity and mortality worldwide, carrying with it significant economic and social burden. COPD is projected by the World Health Organization (WHO) to become the fourth leading cause of death by 2030.

• Medications to treat COPD are used to reduce symptoms and frequency and severity of exacerbations and to improve exercise tolerance and health. There is no evidence that any of the existing COPD medications modify the long-term decline of lung function.

• The classes of medications to treat COPD include beta-agonists (SABAs and LABAs), anticholinergics (long- and short-acting), methylxanthines, corticosteroids, phosphodiesterase-4 inhibitors, mucolytic agents, or a combination of these classes. The choice of medication within each class depends on availability, cost, favorable clinical response, and side effects. Therapy should be individualized.

• Other long-action beta₂-agonist/antimuscarinic combinations include formoterol/glycopyrrolate (Bevespi Aerosphere™), indacaterol/glycopyrrolate (Utibron™ Neohaler®), tiotropium/olodaterol (Stiolto™ Respimat®), and umeclidinium/vilanterol (Anoro® Ellipta®).

• According to the 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines:
  – Inhaled bronchodilators in COPD are central to symptom management and are given to prevent or reduce symptoms (Evidence A).
  – LABA and long-acting antimuscarinic antagonists (LAMAs) significantly improve health status, lung function, and dyspnea and reduce exacerbation rates (Evidence A).
  – LABAs and LAMAs are preferred over short-acting medications, except in patients with only sporadic dyspnea (Evidence A) and for immediate symptom relief for those already on maintenance, long-acting bronchodilators.
  – Patients can be initiated on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. For those started on single therapy but who continue to have persistent dyspnea, dual therapy should be started (Evidence A).
  – Compared to LABAs, LAMAs have a greater effect on exacerbation reduction (Evidence A) and decrease hospitalizations (Evidence B).
  – A LABA/LAMA combination treatment increases FEV₁ and reduces symptoms (Evidence A) and exacerbations (Evidence B) compared to monotherapy.

• When assessing initial pharmacological treatment options for patients in Groups A, B, C, and D, aclidinium bromide/formoterol fumarate may be an option starting in Group B. Aclidinium bromide/formoterol fumarate (Duaklir Pressair), offers a fixed-dose LAMA/LABA twice-daily dry powder inhaler, for COPD maintenance. It is not indicated for the relief of acute bronchospasm or for asthma.

• Circassia plans to launch the product in the second half of 2019.
SUGGESTED UTILIZATION MANAGEMENT

<table>
<thead>
<tr>
<th>Anticipated Therapeutic Class Review (TCR) Placement</th>
<th>Chronic obstructive pulmonary disease (COPD) Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Edit</strong></td>
<td><strong>Initial Approval Criteria</strong></td>
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<tr>
<td></td>
<td>• Patient is ≥ 18 years old; <strong>AND</strong></td>
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<td></td>
<td>• Patient has a diagnosis of COPD; <strong>AND</strong></td>
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<td></td>
<td>• Patient is not using the medication for asthma or for acute relief of bronchospasm; <strong>AND</strong></td>
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<td></td>
<td>• Patient is not experiencing acutely deteriorating COPD; <strong>AND</strong></td>
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<tr>
<td></td>
<td>• Patient does not have a history of hypersensitivity to aclidinium bromide or formoterol fumarate or to any component of the product, including milk proteins; <strong>AND</strong></td>
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<tr>
<td></td>
<td>• Patient is not taking another long-acting beta agonist (LABA)</td>
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<tr>
<td><strong>Renewal Criteria</strong></td>
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<tr>
<td></td>
<td>• Patient continues to meet initial criteria; <strong>AND</strong></td>
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<tr>
<td></td>
<td>• Patient is experiencing COPD symptom improvement or maintenance; <strong>AND</strong></td>
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<tr>
<td></td>
<td>• The patient is not experiencing any treatment-limiting adverse reactions of the medication</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Quantity Limit</th>
<th>60 metered doses/month</th>
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</thead>
<tbody>
<tr>
<td><strong>Duration of Approval</strong></td>
<td>1 year for initial and renewal</td>
</tr>
<tr>
<td><strong>Drug to Disease Hard Edit</strong></td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td>Milk protein allergy</td>
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</tbody>
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REFERENCES