

Almirall's acclidinium bromide/formoterol fumarate recommended for approval in Europe to treat COPD

- **Positive CHMP opinion is an important step in making this new respiratory therapy available to treat Chronic Obstructive Pulmonary Disease (COPD)**
- **Marketing authorisation in the European Union is expected before the end of the year**
- **Acclidinium/Formoterol will be marketed in Europe under the trademarks Duaklir[®] Genuair[®] and Brimica[®] Genuair[®]**

Barcelona, September, 25 2014. - Almirall S.A. (ALM) announced today that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has issued a positive opinion for the regulatory approval of Duaklir[®] Genuair[®] (acclidinium bromide/formoterol fumarate) in all EU member states as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).¹

Acclidinium bromide/formoterol fumarate is a fixed dose combination of two approved long-acting bronchodilators. Acclidinium bromide is a novel anticholinergic or long acting muscarinic antagonist (LAMA). Formoterol fumarate is a long-acting beta-agonist (LABA).²

As part of its assessment, CHMP reviewed efficacy and safety data of acclidinium bromide/formoterol fumarate BID from more than 2,000 patients. The clinical program included 11 clinical studies conducted in 29 countries worldwide.²

"We are very pleased with the CHMP positive recommendation for acclidinium bromide/formoterol fumarate" said Thomas Eichholtz, Chief Scientific Officer at Almirall. "The Committee's positive opinion today marks a significant step forward in bringing this new treatment option to patients with COPD."

In the EU, the European Commission generally follows the recommendations of the CHMP (EMA) and delivers its final decision within three months after the CHMP recommendation. The decision will be applicable to all 28 EU member states plus Iceland and Norway. Acclidinium bromide/formoterol fumarate will be marketed in Europe by Almirall under the trade name Duaklir[®] Genuair[®] and Brimica[®] Genuair[®].

Almirall's respiratory franchise is complemented by acclidinium bromide, a long-acting inhaled muscarinic receptor antagonist (LAMA) for COPD. Acclidinium bromide was approved by the EMA and by the US Food and Drug Administration (FDA) in 2012 and is available in 24 countries marketed under the trade names Eklira[®] Genuair[®], Bretaris[®] Genuair[®], Tudorza[™] Pressair[™] and Tudorza[™] Genuair[™]. Further compounds in development include abediterol, a novel long acting beta-2 adrenergic agonist (LABA) for asthma and COPD, two novel dual action long-acting muscarinic antagonist beta-2 agonist MABA compounds plus PAN-JAK and PI3K δ inhibitors.

End notes

Acclidinium bromide/formoterol fumarate scientific evidence²

Bronchodilation

Acclidinium bromide/formoterol fumarate 340/12 micrograms twice daily consistently provided clinically meaningful improvements in lung function (as assessed by FEV₁, forced vital capacity and inspiratory capacity) compared with placebo. In Phase III studies, clinically meaningful bronchodilator effects were seen within 5 minutes of the first dose and were maintained over the dosing interval. There was a sustained effect over time in the six months and one year Phase III studies.^{9,10}

In study ACLIFORM-COPD, acclidinium bromide/formoterol fumarate showed improvements in FEV₁ at 1 hour post-dose relative to placebo and acclidinium of 299 ml and 125 ml, respectively (both $p < 0.0001$) and improvements in trough FEV₁ relative to placebo and formoterol of 143 ml and 85 ml, respectively (both $p < 0.0001$). In study AUGMENT, Acclidinium bromide/formoterol fumarate showed improvements in FEV₁ at 1 hour post-dose relative to placebo and acclidinium of 284 ml and 108 ml (both $p < 0.0001$), respectively, and improvements in trough FEV₁ relative to placebo and formoterol of 130 ml ($p < 0.0001$) and 45 ml ($p = 0.01$), respectively.^{9,10,11}

Breathlessness and other symptomatic outcomes:

Acclidinium bromide/formoterol fumarate provided a clinically meaningful improvement in breathlessness (assessed by the Transition Dyspnoea Index [TDI]) with an improvement in the TDI focal score at 6 months compared to placebo of 1.29 units in study ACLIFORM-COPD ($p < 0.0001$) and 1.44 units in study AUGMENT ($p < 0.0001$). The percentages of patients with clinically meaningful improvements in TDI focal score (defined as an increase of at least 1 unit) were higher with acclidinium bromide/formoterol fumarate than with placebo in ACLIFORM-COPD (64.8% compared to 45.5%; $p < 0.001$) and AUGMENT (58.1% compared to 36.6%; $p < 0.0001$).^{12,13,14}

The pooled analysis of these two studies showed acclidinium bromide/formoterol fumarate to be associated with statistically significant greater improvements in TDI focal score compared to acclidinium (0.4 units, $p = 0.016$) or formoterol (0.5 units, $p = 0.009$). In addition, a higher percentage of patients receiving acclidinium bromide/formoterol fumarate responded with a clinically meaningful improvement in TDI focal score compared to either acclidinium or formoterol (61.9% compared to 55.7% and 57.0%, respectively; $p = 0.056$ and $p = 0.100$, respectively).

Acclidinium bromide/formoterol fumarate improved daily symptoms of COPD such as 'breathlessness', 'chest symptoms', 'cough and sputum' (assessed by E-RS total score) as well as overall night-time symptoms, overall early morning symptoms and symptoms limiting early morning activities compared to placebo, acclidinium and formoterol but the improvements were not always statistically significant.^{15,12}

Health-related quality of life:

Acclidinium bromide/formoterol fumarate provided a clinically meaningful improvement in disease-specific health status (as assessed by the St. George's Respiratory Questionnaire [SGRQ]) in study AUGMENT, with an improvement in the SGRQ total score compared to placebo of -4.35 units ($p < 0.0001$). The percentage of patients in AUGMENT who achieved a clinically meaningful improvement from baseline in SGRQ total score (defined as a decrease of at least 4 units) was higher with acclidinium and formoterol than with placebo (58.2% compared to 38.7%, respectively; $p < 0.001$). In study ACLIFORM-COPD, only a small decrease in SGRQ total score compared to placebo was observed due to an unexpectedly large placebo response ($p = 0.598$) and the percentages of patients who

achieved clinically meaningful improvements from baseline were 55.3% with aclidinium bromide/formoterol and 53.2% with placebo (p=0.669).^{13,14,16}

In the pooled analysis of the two 6-month Phase III studies, aclidinium bromide/formoterol showed greater improvements in SGRQ total score compared to formoterol (-1.7 units; p=0.018) or aclidinium (-0.79 units, p=0.273). In addition, a higher percentage of patients receiving aclidinium bromide/formoterol responded with a clinically meaningful improvement in SGRQ total score compared to aclidinium and formoterol (56.6% compared to 53.9% and 52.2%, respectively; p=0.603 and p=0.270, respectively).

Exacerbations

Pooled efficacy analysis of the two 6-month Phase III studies demonstrated a statistically significant reduction of 29% in the rate of moderate or severe exacerbations (requiring treatment with antibiotics or corticosteroids or resulting in hospitalisations) with aclidinium bromide/formoterol compared to placebo (rates per patient per year: 0.29 vs. 0.42, respectively; p=0.036).¹⁷

In addition, aclidinium bromide/formoterol statistically significantly delayed the time to first moderate or severe exacerbation compared to placebo (hazard ratio=0.70; p=0.027).

Use of rescue medication

Aclidinium bromide/formoterol reduced the use of rescue medication over 6 months compared to placebo (by 0.9 puffs per day [p<0.0001]), aclidinium (by 0.4 puffs/day [p<0.001]) and formoterol (by 0.2 puffs/day [p=0.062]).

Side effects

Adverse reactions associated with aclidinium bromide/formoterol were similar to those of the individual components. As aclidinium bromide/formoterol contains aclidinium and formoterol, the type and severity of adverse reactions associated with each of the components may be expected with aclidinium bromide/formoterol.^{18,19,20}

More information:

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About aclidinium bromide/formoterol fumarate

Aclidinium bromide/formoterol fumarate (400/12mcg) is a fixed dose combination of two approved long-acting bronchodilators with different mechanisms of action and similar pharmacodynamic profiles. Aclidinium bromide is an anticholinergic or long acting muscarinic antagonist (LAMA) that produces bronchodilation by inhibiting the muscarinic M3 receptor in the airway smooth muscle. Formoterol fumarate is a long-acting beta-agonist (LABA) that stimulates the B2-receptors in the bronchial smooth muscle resulting in bronchodilation. Both aclidinium bromide (Elkira[®] / Bretaris[®] / Tudorza[™]) and formoterol fumarate are separately approved for the maintenance treatment of COPD in the United States and Europe.

About Pressair™/Genuair®

Genuair® is a multi-dose dry powder inhaler which is pre-loaded with the required doses, for one month of treatment, and ready to use. Findings of a recent publication suggest that poor adherence to inhaled therapies is common among patients with asthma and COPD. Pressair™/Genuair® was designed with a double feedback system: per our instructions for use: a 'click' sounds when the patient is inhaling correctly and a control coloured window changes from green (ready to use) to red when the patient inhaled correctly. Moreover, the device incorporates safety features such as a visible dose indicator to show patient approximately how many doses remain, an anti-double-dosing mechanism and an end-of-dose lock-out system to prevent use of an empty inhaler.

About COPD

Chronic Obstruction Pulmonary Disease (COPD), or chronic obstructive pulmonary disease, is a common, progressive, and debilitating lung disease characterized by persistent airflow limitation that makes it hard to breathe. The World Health Organization (WHO) has described COPD as a global epidemic; an estimated 64 million people have COPD worldwide. More than 3 million people died of the condition in 2005, which is equal to 5% of all deaths globally that year. Total deaths from COPD are projected to increase by more than 30% in the next 10 years without interventions to cut risks, particularly exposure to tobacco smoke.³ WHO predicts that COPD will become the third leading cause of death worldwide by 2030.⁴ COPD is already the fourth leading cause of death in the U.S.⁵

In patients with COPD the airways in the lungs typically lose their elasticity, produce excess mucus and become thick and inflamed, limiting the passage of air. The most common symptoms of COPD are breathlessness (or a "need for air"), abnormal sputum (a mix of saliva and mucus in the airway), and chronic cough. As the condition worsens and breathlessness increases, daily activities, such as walking up a short flight of stairs or carrying a suitcase, can become very difficult. New therapies to treat this debilitating disease may be of value.

COPD has historically been seen as a disease that affects old men, despite the fact that nowadays 44% of patients are women.⁶

In addition to the impact of the disease on a patient's quality of life, COPD poses a significant financial burden to society. Among respiratory diseases, COPD is the leading cause of lost work days.⁷

Although COPD is not curable, treatment can help control the symptoms and increase a patient's quality of life.³ For example, bronchodilator medications are central to the symptomatic management of COPD, and the combination of a LAMA and a LABA (aclidinium + formoterol) as a treatment option for COPD patients, which act through different mechanisms of action, provides improved bronchodilation and symptom control compared to that achieved with either bronchodilator alone.^{2,8}

About Almirall

Almirall is a global company based in Barcelona dedicated to providing valuable medicines through its R&D, agreements and alliances. Our work covers the whole of the drug value chain. A consolidated profitable growth allows us to devote our talent and efforts in the respiratory and dermatology areas, with a focused interest in gastroenterology and pain. Our size enables us to be agile and flexible so that we can accomplish the purpose of taking our innovative products wherever they are needed.

Founded in 1943, Almirall is listed on the Spanish Stock Exchange (ticker: ALM) and it has become a source of value creation for society due to its vision and the commitment of its long-standing major shareholders. In 2013, its revenues totaled 825 million euros and, with

more than 3,000 employees, it has gradually built up a trusted presence across Europe, as well as in the US, Canada and Mexico.

For more information please visit www.almirall.com

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