Eklira®/Bretaris® Genuair® (aclidinium bromide) approved in Europe for the maintenance treatment of Chronic Obstructive Pulmonary Disease (COPD)

- **Aclidinium provides significant and sustained bronchodilation from the first dose. It also improves symptoms control and patients' quality of life**[1]

- **COPD is a debilitating disease which is one of the most common causes of death in Europe. Patients suffer from difficulties to breathe, limitations in activities, poor quality of life and chronic cough and sputum**

- **Aclidinium is a long acting muscarinic antagonist (LAMA) developed by Almirall's R&D. First launches are planned in Europe later this year**

Barcelona, July, 24th 2012 - Almirall S.A. (ALM) announced today that the European Commission has granted marketing approval to Eklira/Bretaris Genuair® (aclidinium 322µg twice daily) in all EU member states, plus Iceland and Norway, as a maintenance bronchodilator treatment to relieve symptoms in adult patients with Chronic Obstructive Pulmonary Disease (COPD), following the positive recommendation received from the CHMP in May this year.

"Patients with COPD have a high symptom burden, which can have important effects on their quality of life", commented Professor Paul W Jones, from St George's Hospital, University of London, and principal investigator of the ATTAIN phase III study. *"The European approval of aclidinium is good news for the healthcare community because improvements observed in health status and symptoms within the trials can finally be translated into benefits for patients in every-day's practice"*, he added.

Clinical efficacy studies showed that aclidinium provides around the clock significant and sustained bronchodilation from the first dose. This benefit was evident within 30 minutes of the first dose. It also reduced moderate and severe exacerbations by approximately 30%. Patients treated with aclidinium needed less rescue medication than patients treated with placebo (p=0.005). It also improved COPD symptoms such as dyspnoea, cough and sputum production.[1,2]

In addition the studies demonstrated that aclidinium provided clinically meaningful improvements in breathlessness (assessed using the Transition Dyspnoea Index [TDI][3]) and disease-specific health status (assessed using the St. George's Respiratory Questionnaire [SGRQ][4]).

"Almirall and its European partner Menarini are pleased with the approval of Eklira/Bretaris Genuair®, an important milestone in Almirall's respiratory franchise, one of our key R&D areas" said Eduardo Sanchiz, Chief Executive Officer, Almirall. "*We are convinced from our large set of scientific data that aclidinium will help patients in Europe to reduce COPD symptoms and improve their quality of life".*

Aclidinium showed a good safety profile, with the most frequently reported adverse reactions being headache (6.6%) and nasopharyngitis (5.5%). Importantly, the incidence of typical anticholinergic adverse events was low and comparable to placebo (e.g. dry mouth and constipation were both <1%).[1]

Menarini will have joint commercialisation rights across the majority of EU member states (excluding the UK, the Netherlands and the Nordic countries where Almirall retains sole marketing rights for the product) as well as Russia, Turkey and other CIS countries under the brand name Bretaris® Genuair®, whilst Almirall will market the product in Europe as Eklira® Genuair®.

Aclidinium is being developed worldwide and has been recently approved in the USA by the FDA where it will be marketed by Forest Laboratories and marketed under the name of Tudorza™ Pressair™. In Japan the product is in development in partnership with Kyorin and with Daewoong in Korea. Almirall holds the rights for the rest of the world.

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Scientific evidence

The aclidinium Phase III clinical development programme included 269 patients treated with aclidinium 322 µg twice daily in one 6-month randomised, placebo-controlled study and 190 patients treated with aclidinium 322 µg twice daily in one 3-month randomised, placebo-controlled study. Efficacy was assessed by measures of lung function and symptomatic outcomes such as breathlessness, disease-specific health status, use of rescue medication and occurrence of exacerbations. In the long-term safety studies, Aclidinium was associated with bronchodilatory efficacy when administered over a 1-year treatment period.

Bronchodilation

In the 6 month study, patients receiving Aclidinium 322 µg twice daily experienced a clinically meaningful improvement in their lung function (as measured by FEV1). Significant bronchodilatory effects were evident from day one and were maintained over the 6-month treatment period. After 6 months treatment, the mean improvement in morning pre-dose (trough) FEV1 compared to placebo was 128 mL (95% CI=85 170; $p<0.0001$). Similar observations were made with Aclidinium in the 3 month study.

Disease-Specific Health Status and Symptomatic Benefits

Aclidinium provided clinically meaningful improvements in breathlessness (assessed using the Transition Dyspnoea Index [TDI]): mean changes vs baseline =1 unit ($p<0.001$) and disease-specific health status (assessed using the St. George's Respiratory Questionnaire [SGRQ]): mean change vs baseline -4.6 units ($p<0.0001$).

Patients treated with aclidinium required less rescue medication than patients treated with placebo (a reduction of 0.95 puffs per day at 6 months [$p=0.005$]). Aclidinium also improved daily symptoms of COPD (dyspnoea, cough and sputum production) and night-time and early morning symptoms.

Reduction in the rate of Moderate to Severe Exacerbations

Pooled efficacy analysis of the 6-month and 3-month placebo controlled studies demonstrated a statistically significant reduction in the rate of moderate to severe exacerbations (requiring treatment with antibiotics or corticosteroids or resulting in hospitalisations) with aclidinium 322 µg twice daily compared to placebo (rate per patient per year: 0.31 vs 0.44 respectively; $p=0.0149$).[2]

Absorption
Aclidinium bromide is rapidly absorbed from the lung, achieving maximum plasma concentrations within 5 minutes of inhalation in healthy subjects, and normally within the first 15 minutes in COPD patients. The fraction of the inhaled dose that reaches the systemic circulation as unchanged aclidinium is very low at less than 5%.

About the Genuair® inhaler
Aclidinium is administered to patients using the novel multidose dry powder inhaler (MDPI), Genuair®. The inhaler comes loaded and assembled and ready for immediate use. Almirall's inhaler was designed with a "click and colour" feedback system which, through a 'colour control window' and an 'audible click', indicates that the patient has inhaled the dose correctly. It also incorporates significant safety features such as a visible dose indicator, an anti-double-dosing mechanism and an end-of-dose lock-out system to prevent use of an empty inhaler.

About COPD
COPD is the occurrence of chronic bronchitis or emphysema, a pair of commonly co-existing diseases of the lungs in which the airways become narrowed. This leads to a limitation of the flow of air to and from the lungs, causing shortness of breath (dyspnoea). In clinical practice, COPD is defined by its characteristically low airflow on lung function tests.

The most common symptoms of COPD are breathlessness (an increased effort to breathe), heaviness or a 'need for air', excessive mucus, and a chronic cough. Some people feel they are gasping for breath. These symptoms get worse when exercising, in case of a respiratory infection or during an exacerbation – periods of time when there is a sudden increase in symptoms and the disease is worse. COPD affects the ability to breathe and is a progressive disease, which means that COPD gets worse over time. Daily activities may become more difficult as the disease worsens. There are significant unmet needs in the treatment of COPD and new therapies may be of value.

The World Health Organization (WHO) has described COPD as a global epidemic, and it is estimated that 210 million people suffer COPD[4] worldwide.

In the European Union, the total direct costs of respiratory diseases are estimated to be approximately 6% of the total healthcare budget, with COPD accounting for more than half (56%) of this expenditure, equating to €38.6 billion. Approximately 200,000–300,000 people die each year in Europe because of COPD[5]. Patients experiencing frequent exacerbations are at risk of increased morbidity and mortality, a faster decline in lung function, and poorer health status.

In the EU, approximately 41.3% lost work days are due to COPD every year and productivity losses due to COPD amount to a total of €28.5 billion annually.

About Almirall
Almirall is an international pharmaceutical company based on innovation and committed to health. Headquartered in Barcelona, it researches, develops, manufactures and commercialises its own R&D and licensed drugs with the aim of improving people's health and wellbeing. Almirall focuses its research resources on respiratory, gastrointestinal, dermatology and pain. Almirall's products are currently present in over 70 countries in the five continents. It has direct presence in Europe and Mexico through 12 affiliates.

Almirall's respiratory franchise is complemented by aclidinium combination products for COPD, currently in late stage development and abediterol (a once daily LABA combined

with an ICS) for asthma and COPD, currently under development, set to move into Phase IIb development worldwide (excluding USA).

For further information please visit: www.almirall.com

References

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[5] Global Initiative for Chronic Obstructive Lung Disease 2011