Almirall's aclidinium 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 and the USA is expected in 2012**
- **Aclidinium will be marketed in Europe under the trademarks Eklira® Genuair® and Bretaris® Genuair®**

Barcelona, May, 28 2012.- 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 Eklira® Genuair® (aclidinium) in all EU member states as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).[1]

"The Committee's positive opinion today marks a significant step forward in bringing to prescribers and patients this novel treatment from Almirall's discovery, and validates the strong data supporting aclidinium's efficacy and safety in treating COPD" said Bertil Lindmark, Chief Scientific Officer at Almirall. *"This positive opinion also supports Almirall's commitment to respiratory research which is set to deliver a robust pipeline of further drugs currently in development."*

As part of its assessment, CHMP reviewed efficacy and safety data of aclidinium BID from more than 2,500 patients. The clinical program included 26 clinical studies conducted in 26 countries worldwide. The CHMP also assessed the Genuair® Inhaler, the Almirall's proprietary multidose dry powder inhaler.

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 27 EU member states plus Iceland and Norway. Aclidinium will be marketed in Europe by Almirall under the trade name Eklira® Genuair®.

Almirall recently signed a license agreement granting Menarini joint commercialisation rights across the majority of EU member states as well as Russia, Turkey and other CIS countries; this deal excludes the UK, the Netherlands and the Nordic countries. Menarini will market the product under the trade name Bretaris® Genuair®.

Aclidinium is also undergoing regulatory assessment in the USA by the Food and Drug Administration (FDA) and approval is expected in 2012.

Regulatory approval of Eklira® Genuair® would pave the way for the subsequent introduction of Almirall's combination products for COPD, currently in late stage development.

Almirall's respiratory franchise is complemented by 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).

End notes

Aclidinium scientific evidence [2]

Bronchodilation
Clinical efficacy studies showed that aclidinium 322 µg[3] twice daily provided clinically meaningful improvements in lung function (as measured by the forced expiratory volume in 1 second [FEV1] which is the most air a person can breathe out in one second) over 12 hours following morning and evening administration, which were evident within 30 minutes of the first dose (increases from baseline of 124-133 ml). The maximal bronchodilation was achieved within 1-3 hours after dosing with mean peak improvements in FEV1 relative to baseline of 227-268 ml at steady state.

Maximal 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 the product in the 3 month study. In the long-term safety studies, Eklira® Genuair® was associated with bronchodilatory efficacy when administered over a 1-year treatment period.

Quality of life
Aclidinium also provided clinically meaningful improvements in breathlessness (assessed using the Transition Dyspnoea Index [TDI]) of 1 unit vs baseline (p<0.001)[4]and disease-specific health status (assessed using the St. George's Respiratory Questionnaire [SGRQ]) with mean improvement vs baseline of 4.6 units (p<0.0001) after six months of treatment[5].

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[3] twice daily compared to placebo (rate per patient per year: 0.31 vs 0.44 respectively; p=0.0149).

Side effects
The most frequently reported adverse reactions with aclidinium 322 µg were headache (6.6%) and nasopharyngitis (5.5%). Also, the incidence of other anticholinergic adverse events was low and comparable to placebo (e.g. dry mouth and constipation were both <1%).

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About aclidinium and the Genuair® inhaler
Aclidinium is a novel, long-acting inhaled muscarinic antagonist (sometimes referred to as an anticholinergic) that has a long residence time at M3 receptors and a shorter residence time at M2 receptors. When given by inhalation, aclidinium leads to bronchodilation by inhibiting airway smooth muscle contraction. Aclidinium bromide is rapidly hydrolysed in human plasma to two major inactive metabolites.

Aclidinium was administered to patients in the trial using a novel, user-friendly multidose dry powder inhaler (MDPI), Genuair®. 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.

Almirall has licensed US rights for aclidinium to Forest Laboratories, Inc., to Kyorin Pharmaceutical Co. Ltd for Japan and to Daewoong Pharmaceutical Co. Ltd for Korea. Almirall has recently given rights of joint commercialisation in the majority of European member states and a number of non-EU countries to Menarini. Almirall maintains rights for the rest of the world. Almirall and Forest are jointly involved in the development of the compound.

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[6]. 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[7].

The World Health Organization (WHO) has described COPD as a global epidemic, and it is estimated that 210 million people suffer COPD[8,9] 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.

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.

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.

For further information please visit: www.almirall.com

References

[1] European Medicines Agency

[2] Efficacy and safety of twice-daily aclidinium bromide in COPD patients: The ATTAIN study - Paul W. Jones, et al - Eur Respir J 02255-2011; published ahead of print 2012, doi:10.1183/09031936.00225511
and
Efficacy and Safety of a 12-week Treatment with Twice-daily Aclidinium Bromide in COPD Patients (ACCORD COPD I) Edward M. Kerwin, et al - COPD: Journal of Chronic Obstructive Pulmonary Disease April 2012, Vol. 9, No. 2, Pages 90-101: 90-101

[3] Each delivered dose (the dose leaving the mouthpiece) contains 322 µg of aclidinium which corresponds to a metered dose of 400 µg aclidinium bromide.

[4] Minimum clinically important difference (MCID) of at least 1 unit change in TDI vs placebo - Minimal important difference of the transition dyspnoea index in a multinational clinical trial.-Witek TJ Jr -Eur Respir J. 2003 Feb;21(2):267-72

[5] Minimum clinically important difference (MCID) of at least - 4 units change in SGRQ - COPD: Journal of Chronic Obstructive Pulmonary Disease, 2005, Vol. 2, No. 1 : Pages 75-79 -St. George's Respiratory Questionnaire: MCID-Paul W Jones

[6]National Heart Lung and Blood Institute. U.S. National Institutes of Health. June 1, 2010. http://www.nhlbi.nih.gov/health/health-topics/topics/copd/.

[7]Nathell, L.; Nathell, M.; Malmberg, P.; Larsson, K. (2007). "COPD diagnosis related to different guidelines and spirometry techniques". Respiratory research 8 (1): 89

[8]World Health Organisation. Global Alliance Against Chronic Respiratory Diseases. http://www.who.int/mediacentre/factsheets/fs315/en/index.html (accessed August 18, 2011)

[9]World Health Organisation. World Health Report 2004. Statistical Annex. Annex table 2 and 3: 120-131