



Media Release

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Tracleer receives label extension in the US for the treatment of patients with mildly symptomatic WHO Functional Class II pulmonary arterial hypertension

Tracleer® indication expansion underscores importance of early screening and treatment to improve outcomes

ALLSCHWIL, SWITZERLAND – 10 August 2009 – Actelion Ltd (SIX: ATLN) announced today that the U.S. Food and Drug Administration (FDA) has approved the company's supplemental New Drug Application (sNDA) for Tracleer® (bosentan) to treat patients with mildly symptomatic WHO Functional Class II (FC II) pulmonary arterial hypertension (PAH). The U.S. FDA has also approved Actelion's Risk Evaluation and Mitigation Strategy (REMS) for Tracleer®.

Jean-Paul Clozel, M.D. and Chief Executive Officer of Actelion commented: "Physicians in the United States of America who treat PAH patients now have access to Tracleer® as an approved therapy for patients not only in advanced, but also in the early stages of this rapidly progressing and life-threatening disease. This label extension is based on EARLY, the only randomized, double blind, placebo controlled study in this mildly symptomatic patient population. The EARLY results demonstrate that Tracleer® significantly reduces risk of clinical worsening in early-stage patients, thereby slowing down disease progression."

Vallerie McLaughlin, MD, Associate Professor of Medicine, Director, Pulmonary Hypertension Program, University of Michigan Health System added: "PAH is a progressive and devastating disease, and patients are not always treated as early as they should be with therapies that can impact disease progression. The approval of Tracleer® for the treatment of patients with early-stage disease, offers physicians a new, proven therapy that may result in beneficial clinical outcomes."

Kirk Taylor, M.D., Senior Vice President, U.S. Medical Group at Actelion Pharmaceuticals US, Inc. commented: "The FDA's approval of Tracleer® for use in patients with early-stage

PAH provides the opportunity to improve clinical outcomes. Tracleer® is the only PAH medication that has consistently shown significantly reduced risk of clinical worsening in PAH patients in three separate Phase III studies.”

Tracleer® is an oral dual endothelin receptor antagonist approved for the treatment of PAH FC II, III and IV in the US [1] and for the treatment of PAH FC II and III in the EU. [2] The company is working with authorities on a worldwide basis to expand the label for Tracleer® to include patients with FC II PAH.

Survey highlights benefits of treating patients with early treatment

Results from a 2008 Harris Interactive survey [3] showed that more than 90 percent of US physicians who treat pulmonary arterial hypertension (PAH) patients believe that the disease is often diagnosed and treated later than it should be.

More than three quarters of physicians understand the clinical benefits of treating early, and agree that goals of treatment include delayed time to clinical worsening and improvement across relevant hemodynamic parameters (pulmonary arterial pressure, pulmonary vascular resistance, cardiac resistance and mean right arterial pressure). However, just over half of these physicians were prescribing endothelin receptor antagonists (ERAs) at the time of the survey.

After reviewing the data from the Phase III EARLY study, more than 90 percent of physicians polled in the survey agreed that they would be likely to prescribe Tracleer® alone or in combination therapy for FC II PAH patients.

The survey polled more than 300 US pulmonologists, cardiologists and rheumatologists who have treated more than five PAH patients in the previous 12 months. Additional data garnered from the survey is as follows:

- 94 percent of physicians agree that PAH is diagnosed later than it should be
- 92 percent of physicians believe PAH is treated later than it should be
- 81 percent of physicians agree that early diagnosis and treatment of PAH would provide numerous positive clinical outcomes in this patient population
- 51 percent of physicians currently prescribe pharmacologic treatment for early stage FC II patients
- 66 percent of physicians would consider prescribing ERAs to FC I/II patients

About the pivotal Phase III EARLY study

The objectives of the prospective, randomized, placebo-controlled, multicenter EARLY (Endothelin Antagonist tRial in miLdIY symptomatic PAH patients) trial were to gain more insights into early stage disease and to investigate the effects of bosentan specifically in patients with WHO FC II PAH.

The results from EARLY - published in "*The Lancet*" in June, 2008 [4] - reinforce the relentlessly progressive nature of PAH even in its early stages. This was evident from the placebo group deterioration reflected in the rate of clinical worsening events. The primary endpoints for the EARLY trial were changes in pulmonary vascular resistance (PVR) and exercise capacity as measured by a six minute walk test (6-MWD). Disease progression was assessed by the secondary endpoints, which included time to clinical worsening and WHO Functional Class.

A highly significant reduction of 22.6% in PVR ($p < 0.0001$) and a significant 77% risk reduction in clinical worsening ($p = 0.011$) were seen after 24 weeks of bosentan treatment compared with placebo. Time to clinical worsening, defined by death, hospitalization for PAH and symptomatic progression of PAH, showed that more patients remained stable without signs of deterioration in the bosentan-treated group compared with placebo (3.4% vs. 13.2%, $p = 0.029$). In addition, a significant delay in WHO functional class deterioration was observed in the bosentan group compared with placebo, providing further evidence of delayed disease progression.

Although the improvement in 6-MWD did not reach statistical significance ($p = 0.076$) this may reflect the fact that, on average, enrolled patients had a relatively well preserved exercise capacity at baseline, which can be more difficult to improve. A subgroup of patients who received concomitant sildenafil showed improvements in the bosentan treatment group consistent with the overall results. The safety and tolerability profile of bosentan was consistent with that observed in previous placebo-controlled clinical trials.

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Notes to the editor:

About Pulmonary Arterial Hypertension (PAH)

Pulmonary arterial hypertension (PAH) is a chronic, life-threatening disorder characterized by abnormally high blood pressure in the arteries between the heart and lungs of an affected individual. The function of the heart and lungs is severely compromised, manifested by a limited exercise capacity, and, ultimately, a reduced life expectancy. Approximately 100,000 people in Europe and the United States are afflicted with either primary or secondary forms of the disease related to conditions or tissue disorders that affect the lungs, such as scleroderma, lupus, HIV/AIDS or congenital heart disease.

PAH is associated with structural changes in both the pulmonary vasculature and the right ventricle. Recent advances [5] in the understanding of the pathogenic factors leading to the pulmonary vascular disease have led to the development of new therapies targeting specific pathways (the prostacyclin pathway; the endothelin pathway; and the nitric oxide pathway) [6]. The available therapies have shown positive treatment effects in patients with PAH, but they do not provide a cure, and in many patients the disease will progress. PAH remains a serious life-threatening condition [6,7]. Early recognition and an understanding of the selection and timing of therapeutic options remain critical elements in the optimal management of patients with this disorder.

About Tracleer® in Pulmonary Arterial Hypertension (PAH)

Tracleer® (bosentan), the first oral dual endothelin receptor antagonist, is approved for the treatment of pulmonary arterial hypertension (PAH) and made available by Actelion subsidiaries in the United States, the European Union, Japan, Australia, Canada, Switzerland and other markets worldwide.

Requires attention to significant safety concerns: Potential for serious liver injury (including rare cases of liver failure and unexplained hepatic cirrhosis in a setting of close monitoring) - Liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter. **High potential for major birth defects** -Pregnancy must be excluded and prevented by two forms of birth control; monthly pregnancy tests should be obtained. Tracleer® is contraindicated for use with cyclosporine A and glyburide. Due to these risks, in the US, Tracleer® is only supplied through a controlled distribution.

References

1. Tracleer® Prescribing Information
2. Tracleer® Summary of Product Characteristics
3. Online survey conducted by Harris Interactive, May 16-22, 2008, among 303 U.S. pulmonologists, cardiologists and rheumatologists who treated at least 5 PAH patients in the previous 12 months. Survey was commissioned by Actelion.
4. Galiè N, Rubin LJ, Hoeper MM, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008;371:2093-100.
5. Farber HW; Loscalzo J. Mechanisms of disease: pulmonary arterial hypertension. *N. Eng. J. Med.* 2004; 351:1655-65.
6. Humbert M; Sitbon O; Simonneau G. Treatment of pulmonary arterial hypertension. *N. Eng. J. Med.* 2004;351:1425-36.
7. Humbert M; Morrell NW; Archer SL; et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. *J. Am. Coll. Cardiol.* 2004; 43: Suppl. 12: 13S-24S.

Actelion Ltd

Actelion Ltd is a biopharmaceutical company with its corporate headquarters in Allschwil/Basel, Switzerland. Actelion's first drug Tracleer®, an orally available dual endothelin receptor antagonist, has been approved as a therapy for pulmonary arterial hypertension. Actelion markets Tracleer® through its own subsidiaries in key markets worldwide, including the United States (based in South San Francisco), the European Union, Japan, Canada, Australia and Switzerland. Actelion, founded in late 1997, is a leading player in innovative science related to the endothelium - the single layer of cells separating every blood vessel from the blood stream. Actelion's over 2000 employees focus on the discovery, development and marketing of innovative drugs for significant unmet medical needs. Actelion shares are traded on the SIX Swiss Exchange (ticker symbol: ATLN) as part of the Swiss blue-chip index SMI (Swiss Market Index SMI®).

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