Medical Media Release

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Tracleer® (bosentan) EU labelling updated to reflect new data in PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology

ALLSCHWIL, SWITZERLAND – <Date> 2006 – Actelion Ltd (SWX: ATLN) announced today that Tracleer® (bosentan) tablets, the orally active dual endothelin receptor antagonist, has received approval for an updated label, which reflects new data for PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology.

The upgrade is based on data from the BREATHE-5 study (**B**osentan **R**andomized trial of **E**ndothelin **A**ntagonist **THE**rapy-5) published in *Circulation* earlier this year.[1] BREATHE-5, investigated 54 patients with Eisenmenger's physiology over a 16 week period and is the first ever multi-centre, randomized, double blind, placebo-controlled study conducted in this group of patients to show treatment benefit.[1]

Eisenmenger's physiology is the most advanced form of PAH related to congenital heart disease. Exercise capacity in these patients is particularly poor even in comparison to other forms of congenital heart disease and is associated with organ damage and a higher likelihood of premature death.[2]

It is very encouraging that bosentan showed a rapid improvement in exercise capacity and functional class in these highly compromised and difficult to treat CHD patients.

In addition to this change in the bosentan SPC, information on the efficacy and safety of using bosentan in patients with PAH associated with HIV has been added to the SPC. This addition is based on data from the BREATHE-4 study.

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References

1. Galie N *et al*. Bosentan therapy in patients with Eisenmenger syndrome: a multi-centre, double-blind randomized placebo-controlled study. *Circulation* 2006; 114: 48-54
2. Diller GP *et al.* Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation*. 2005;112:828-35.
3. Tracleer SPC

About BREATHE-5

BREATHE-5 was the first trial designed as a multi-centre, double-blind, randomised (2:1), placebo-controlled study to assess the effects of bosentan on systemic oxygen saturation, pulmonary and systemic haemodynamics and exercise capacity in patients with Eisenmenger's syndrome

Fifty-four patients were randomised 2:1 to bosentan (n=37) or placebo (n=17) for 16 weeks. The trial was conducted in 15 centres in Europe, North America and Australia.

About Eisenmenger's physiology

Eisenmenger's physiology is a progressive heart condition and occurs in people who have a congenital heart defect or 'hole in the heart'. Prior to the development of Eisenmenger's physiology, the heart defect allows blood to flow from the left ventricle to the right (left-to-right shunt), which increases blood flow through the lungs. Over time damage to the pulmonary vessels causes increased resistance to the blood flow to the lungs (pulmonary hypertension) leading to a reversal of the shunt, with blood flowing from the right to the left side. This phenomenon of pulmonary hypertension and right to left shunting is termed 'Eisenmenger's syndrome', or 'Eisenmenger's physiology'.

This flow of blood from the right to the left causes the most recognizable symptom of Eisenmenger's physiology, a blue tinge to the skin (cyanosis) resulting from low blood oxygen concentration.

About BREATHE-4

In the multicenter, multinational, open-label, non-comparative, phase IIIb trial BREATHE-4 (Bosentan Randomized trial of Endothelin Antagonist THErapy for Pulmonary Hypertension-4), the safety and efficacy of Tracleer(R) (bosentan) was evaluated over a time period of 16 weeks in 16 patients with PAH related to HIV infection. The initial sample size was 30 patients, but enrolment was concluded early as the positive results observed were felt by the investigators to be of clinical relevance and merit immediate reporting. Efficacy was measured as change in hemodynamics, exercise capacity (6-minute walk test), clinical worsening and WHO functional class compared to baseline. Safety was evaluated, using standard safety assessments (liver function tests) with additional routine evaluation of HIV status (CD4 cell count and viral load).