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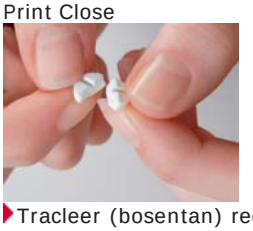

Tracleer (bosentan) receives EU approval for pediatric formulation – the first and only licensed pulmonary arterial hypertension therapy for children

Mon, Jul 6, 2009 written by IR & Corporate Communication

ALLSCHWIL, SWITZERLAND – 06 July 2009 – Actelion Ltd (SIX: ATLN) announced today that the pediatric dispersible formulation of Tracleer® (bosentan) for the treatment of pulmonary arterial hypertension (PAH) in children has been approved in the European Union. More...

This approval makes Tracleer® the only PAH therapy with an approved pediatric formulation for treating children from two years of age. PAH is a severe condition in children with an estimated median survival of 10 months after diagnosis if left untreated [1].

Martine Clozel, M.D., Pediatrician and Chief Scientific Officer at Actelion, commented: “Our team is very proud of this achievement. We decided very early in the development of Tracleer® to devote time and effort to the development of a formulation adapted to the daily treatment of children suffering from PAH, even if it was representing a small population. It has been a long, but ultimately extremely rewarding journey, which had begun even before the first marketing authorization of Tracleer®.”

Isaac Kobrin, M.D., Chief Medical Officer at Actelion, added: “Having the approval of Tracleer®, with an accurate dosing in a child-friendly form, is an important advancement in the treatment of PAH in children. After receiving approval in the EU, we will continue our regulatory filings in other countries to ensure that children can benefit from this pediatric formulation of Tracleer® on a worldwide basis.”

Professor Maurice Beghetti, Head of the Pediatric Cardiology Unit at Hôpital des Enfants, Geneva, commented: “It is great to see Actelion leading the way in providing a treatment fully tailored for children, from the precise dosing to the flavor. Ensuring correct dosing for children is a challenge we face across all diseases but particularly in orphan diseases that affect children. This pediatric formulation for Tracleer® is a large step in the right direction towards developing treatment with the needs of children specifically in mind.”

Tracleer® is an oral, dual endothelin receptor antagonist, which is currently approved in Europe for the treatment of PAH; in WHO Functional Class III to improve exercise capacity and symptoms and in WHO Functional Class II where some improvements have also been shown [2]. In the EU, Tracleer® is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

The new quadrisect, dispersible 32mg tablet formulation of bosentan, which was specifically developed for children, allows a convenient, accurate and more flexible dosing regimen according to low body weight.

The safety and tolerability profile of Tracleer® in children was consistent with that observed in previous placebo-controlled clinical trials in the adult population.

The key trials in the pediatric research program include:

- BREATHE-3 (Bosentan Randomized trial of Endothelin Antagonist THErapy for pulmonary hypertension): an open-label study that provided safety and efficacy data in children with PAH treated with Tracleer® with or without concomitant prostanoid therapy. It also provided important information on the dose required in the pediatric formulation.

- FUTURE-1 (Pediatric FormUlation of bosenTan in pUlmonary arterial hypeRtEnsion): an open-label study that evaluated the safety and pharmacokinetics of a new dispersible tablet formulation of Tracleer®. This study provided important pharmacokinetic and dosing information using the new pediatric formulation of bosentan. In FUTURE-1, the observed exposure to Tracleer® was similar to that in children who participated in BREATHE-3.

- FUTURE-2: an open-label safety extension study is ongoing to assess long-term safety and outcome

data.

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Notes to 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 [4] 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) [5]. 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 [5,6]. 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 PAH in Children

PAH is a severe condition in children with an estimated median survival of 10 months after diagnosis, if left untreated [1].

Online information on PAH is available at www.pah-info.com. PAH-info.com is part of an international PAH awareness campaign supported by Actelion Pharmaceuticals and has been created to provide information to healthcare professionals and patients.

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.

About Actelion's pediatric program

BREATHE-3 (Bosentan Randomized trial of Endothelin Antagonist THErapy for pulmonary hypertension) an open-label study, provided safety and efficacy data in children with PAH, treated with the adult film-coated tablet formulation of Tracleer® with or without concomitant prostanoid therapy. It also provided important information on the dose required in the pediatric formulation.

In the BREATHE-3 study, WHO functional class improved in five of the 19 patients over the 12-week treatment period. Improvements were observed in each weight group, and only one patient deteriorated; 13/19 remained stable. These clinical results were consistent with those obtained in earlier studies conducted in adult patients and support that pediatric patients with PAH may derive significant clinical benefit from therapy with bosentan.

FUTURE-1 (Pediatric FormUlation of bosenTan in pUlmonary arterial hypertension) an open-label study, evaluated the safety and pharmacokinetics of a new dispersible tablet formulation of bosentan. A new oral, dispersible, quadrisect tablet formulation of bosentan dedicated to pediatric patients was investigated; patients initially received 2 mg/kg bid for 4 weeks followed by 4 mg/kg bid until Week 12. The trial enrolled 36

patients aged from 2 years up to 12 years with idiopathic PAH or familial PAH.

The main objective was to demonstrate that exposure to the pediatric formulation of bosentan in children with PAH is similar to the known exposure of the adult formulation. The primary study endpoint was AUC(tau) of bosentan, determined at Week 12. Secondary objectives included evaluation of tolerability and safety of bosentan in pediatric patients with PAH. Secondary endpoints included additional pharmacokinetic parameters of Cmax and Tmax. Exploratory endpoints included: changes from baseline to Week 12 in health-related quality of life, WHO functional class, and Global Clinical Impression.

In FUTURE-1, the observed exposure to bosentan was similar to that in children who participated in BREATHE-3. A subset of 11 patients had pharmacokinetics evaluated for both 2 and 4 mg/kg doses. In these patients, exposure to bosentan was comparable at both doses: geometric mean AUC(tau) was 3577 ng x h/mL and 3371 ng x h/mL with bosentan 2 mg/kg and 4 mg/kg, respectively, and geometric mean Cmax was 583 ng/mL and 649 ng/mL, respectively.

The safety and tolerability profile of bosentan was consistent with that observed in previous placebo-controlled clinical trials in the adult population.

An open-label safety extension, FUTURE-2, is ongoing to assess long-term safety and outcome data.

About Tracleer® in Digital Ulcers (DU)

DUs are a manifestation of the underlying vasculopathy which is central to the pathophysiology of systemic sclerosis (SSc) and pivotal in the development of PAH in SSc, one of the leading causes of death in SSc. Endothelin, a pathogenic mediator, is implicated in the underlying vasculopathy in SSc.

DUs can be a frequent, persistent and debilitating complication of SSc. They are caused by a reduction in the lumen of small bloody vessels that decreases blood flow to the fingers and toes causing open sores. DUs are painful, with a debilitating impact on patients' daily life, often making it impossible to work and undertake even simple day-to-day activities, particularly those associated with fingertip function. Reducing the occurrence of new DUs is an important and achievable treatment goal in SSc.

In the EU, Tracleer® is indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease. Tracleer® has been shown to improve hand function (i.e. dressing and hygiene) in patients with scleroderma-induced digital ulcers.

Requires attention to two significant safety concerns [2]: 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. Because of these risks, Tracleer® is only supplied through controlled distribution.

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Author: Andrew Jones